



Epidemiology of Diabetic Retinopathy and an Assessment of Screening Intervals

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A thesis submitted for the fulfilment of the
requirement for the degree of Doctor of Philosophy

Diabetes Research Unit

School of Medicine

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Declaration and Statements

Declaration

This work has not been submitted in substance for any other degree or award at this or any other university or place of learning, nor is being submitted concurrently in candidature for any degree or other award.

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This thesis is being submitted in partial fulfillment of the requirements for the degree of PhD.

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This work is the result of my own independent work/investigation, except where otherwise stated. Other sources are acknowledged by explicit references. The views expressed are my own

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Summary

This thesis was an observational study to retrospectively examine the prevalence and incidence of DR and its associated risk factors from two screening services (Wales and Johannesburg, South Africa) in order to determine safe screening intervals in persons without evidence of DR at initial screening based on digital photography. Between 2005 and 2009 a total of 135,152 persons with diabetes over 12 years of age in Wales were screened. However, a total of 43,759 persons were excluded from analysis as they did not have their type of diabetes recorded (29,807) or where it was recorded it was outside of the pre-specified age at diagnosis of diabetes range of ≥ 30 years for type 2 DM and < 30 years for type 1 DM (13,952). In the Centre for Diabetes and Endocrinology, Johannesburg, South Africa a smaller population of 5,565 were screened between 2001-2010. A total of 50 persons were excluded from this analysis as they had a type of diabetes recorded other than type 1 DM or type 2 DM. Therefore, data from 91,393 (86,390 T2DM, 5,003 T1DM) persons from the Wales screening service and 5,515 (3,978 T2DM, 1,537 T1DM) from South Africa, were analysed.

In Wales, the prevalence of any DR was 31.0%, background DR (BDR) 26.6% and referable DR (RDR) 4.4% in T2DM at baseline. The prevalence was higher in T1DM at 56.2%, 39.8% and 16.4% respectively. Increased duration of diabetes was independently associated with increased prevalence and incidence of any DR, BDR and RDR for T2DM and T1DM as well as treatment modality in T2DM. The four year cumulative incidence of RDR was 1.6% for T2DM and 5.6% for T1DM.

At the Centre for Diabetes and Endocrinology Johannesburg the prevalence of any DR was 21.6%, BDR 14.8% and RDR 6.7% in T2DM at first screening and higher at 36.9%, 27.2% and 9.7% respectively for T1DM. Glycaemic control (HbA_{1c}) and duration of diabetes were significantly associated with the prevalence and incidence of any DR, BDR and RDR in both T2DM and T1DM. Ethnicity and hypertension were also risk factors. The seven year cumulative incidence of RDR was 4.7% for T2DM and 5.0% for T1DM.

Risk factor analysis indicated that the screening intervals could be extended beyond annual based on type of diabetes, duration of diabetes, HbA_{1c} , ethnicity, hypertension and treatment modality in T2DM. This analysis adds to an increasing evidence base for considering extending the screening intervals beyond annually for those at low risk with no DR at initial screening.

Limitations of this study included the need to exclude a high number of persons in order to ensure the quality of the data; the numbers lost to follow up (meaning all results from 3 years should be interpreted with caution) and the fact that the visual impairment and blindness within the programmes could not necessarily all be attributed to DR as recordings of other lesions were not included in the datasets.

Abbreviations

ABCD	Appropriate Blood Pressure Control in Diabetes
ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACE	Angiotensin-Converting Enzyme Inhibitor
ACR	Albumin: Creatinine Ratio
ADVANCE	Action in Diabetes and Vascular disease: preterAx and DiamicroN mr Controlled Evaluation
AGE	Advanced Glycation End-products
ANOVA	Analysis of Variance
BDR	Background Diabetic Retinopathy
CDE	Centre for Diabetes and Endocrinology
CI	Confidence Interval
CSMO	Clinically Significant Macular Oedema
CWS	Cotton Wool Spots
DCCT	Diabetes Control and Complications Trial
DD	Disc Diameter
Diabetes	Diabetes Mellitus
DIRECT	Diabetic Retinopathy Candestan Trials
DR	Diabetic Retinopathy
DRS	Diabetic Retinopathy Study
DRSSW	Diabetic Retinopathy Screening Service for Wales

DRVS	Diabetic Retinopathy and Vitrectomy Study
eGFR	estimated Glomerular Filtration Rate
ERG	Electroretinogram
EQA	External Quality Assurance
ETDRS	Early Treatment Diabetic Retinopathy Study
EURODIAB	The epidemiology and prevention of diabetes
EX	Exudate
FIELD	Fenofibrate Intervention and Event Lowering in Diabetes
GP	General Practitioner
HCA	Health Care Assistant
HDL	High-Density Lipoprotein
HES	Hospital Eye Service
HM	Haemorrhage
HR	Hazard Ratio
HRC	High Risk Characteristics
IGT	Impaired Glucose Tolerance
IGF-1	Insulin like Growth Factor
IQR	Interquartile range
IVTA	Intravitreal Triamcinolone Acetate
IRMA	Intra Retinal Microvascular Abnormality
LADA	Latent Autoimmune Diabetes of Adulthood
LDL	Low-Density Lipoprotein
Ma/A	Microaneurysm

n	number
NICE	National Institute for health and Care Excellence
NM	Non-Mydriatic
No DR	No Diabetic Retinopathy
NPDR	Non-Proliferative Diabetic Retinopathy
NSC	National Screening Committee
NSF	National Service Frameworks
NVD	New Vessels on the optic Disc
NVE	New Vessels Elsewhere
OHA	Oral Hyperglycaemic Agents
OR	Odds Ratio
PDR	Proliferative Diabetic Retinopathy
PKC	Protein Kinase C
PPDR	Pre-Proliferative Diabetic Retinopathy
QA	Quality Assurance
RAS	Renin-Angiotensin System
RDR	Referable Diabetic Retinopathy
SD	Standard Deviation
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
UG	Ungradeable
UKPDS	United Kingdom Prospective Diabetes Study
VA	Visual Acuity

VB	Venous Beading
VDAT	Veterans Affairs Diabetes Trial
VEGF	Vascular Endothelial Growth Factor
WCSDR	Welsh Community Diabetic Retinopathy Study
WESDR	Wisconsin Epidemiologic Study of Diabetic Retinopathy
WHO	World Health Organisation
yrs	years

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Chapter 1

Introduction

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1.1 Introduction

Diabetes mellitus (diabetes) results in considerable morbidity and premature mortality, and is estimated to involve 387 million people worldwide in 2014, with a possible further 46% remaining undiagnosed. (Same 1993, Wild et al. 2004, Al-Rubeaan 2010, International Diabetes Federation 2014) These figures are predicted to rise to 592 million people worldwide by 2035 due to a number of factors including an increased life expectancy, obesity, reduced physical fitness, urbanisation and improved detection. (International Diabetes Federation 2014)

Diabetes is a chronic metabolic disease characterised by hyperglycaemia that results from defects in insulin secretion, absolute or relative and/or insulin action. (American Diabetes Association 2014) The range of pathogenic processes involved include the autoimmune destruction of pancreatic β cells with insulin deficiency and abnormalities in carbohydrate, fat and protein metabolism, resulting in resistance to insulin action. The majority of diabetes falls into two broad categories: type 1 diabetes which is caused by an absolute deficiency of insulin secretion, and type 2 diabetes caused by a combination of resistance to insulin action and an inadequate compensatory insulin secretion response. The majority of persons with diabetes (~90%) will have type 2 diabetes. There are also other types of diabetes which are either secondary to diseases of the exocrine pancreas, and drug or chemically induced; or to other causes such as either to genetic defects in β -cell function and insulin action and gestational diabetes, which is diagnosed during pregnancy and is not clearly diabetes. (American Diabetes Association 2013)

Diabetes has profound effects on the structure and function of many tissues and organs in the body. Complications of diabetes include macrovascular disease - cardiovascular disease such as stroke, myocardial infarction and peripheral

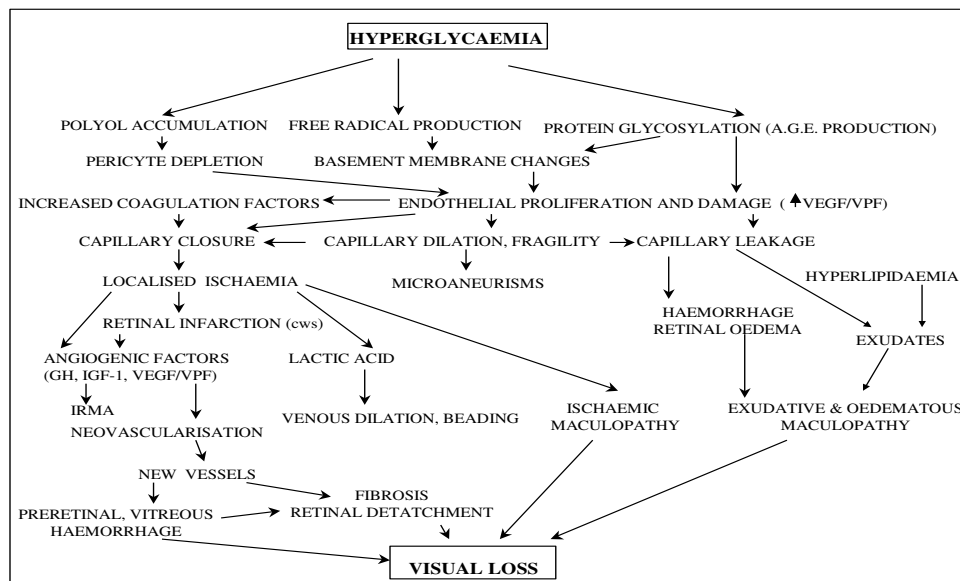
vascular disease, and microvascular disease including diabetic retinopathy (DR), diabetic neuropathy and diabetic kidney disease (diabetic nephropathy). (Holt et al. 2010) The prevalence of these complications is strongly related to the type and duration of diabetes and glycaemic control. Other risk factors for these complications include hypertension, dyslipidaemia and treatment modality. The increasing global population, increasing age and predicted rise in the proportion of adults with diabetes will inevitably be accompanied by an increase in diabetic complications.

Diabetes is a major public health problem and the incidence of blindness is 2-3 times greater in persons with diabetes when compared with the non-diabetic population. (Hayward et al. 2002, Zhang et al. 2008) DR is the most common microvascular complication of diabetes and was until recently regarded as the most prevalent cause of visual impairment in the working age population in developed countries. (Heng et al. 2012) However, a recent report has indicated that in the UK, DR has been overtaken by inherited retinal conditions as the leading cause of blindness in the working age group which the authors suggested was possibly a result of DR screening programmes and improved diabetes care. (Liew et al. 2014) Globally, it is estimated that there are 93 million people with DR, 17 million with proliferative DR (PDR), 21 million with macular oedema and 28 million with sight-threatening DR. (Yau et al. 2012) Visual loss and blindness due to diabetes is essentially preventable in the vast majority of people, through optimal treatment of diabetes, hypertension and hypercholesterolemia and the implementation of screening to detect treatable DR.

1.2 Diabetic retinopathy

Our understanding of the pathophysiological mechanisms underlying the development of DR is constantly evolving.(Ciulla et al. 2003, Antonetti et al. 2006, Curtis et al. 2009) Overall, diabetic microvascular complications are caused by prolonged exposure to high glucose levels.(Giacco F et al. 2010) The extent of tissue damage is also determined by genetic determinants of individual susceptibility and by the presence of such independent accelerating factors as hypertension and dyslipidaemia. Chronic exposure to hyperglycaemia and other causal risk factors (hypertension) is believed to initiate a cascade of biochemical and physiological changes that ultimately lead to neuro-vascular damage and consequently retinal dysfunction,(Cheung et al. 2010) (Figure 1.2.1).

Figure 1.2.1: Physico-chemical mechanisms in the evolution of DR. Reproduced with permission from (Gibbins 1999)

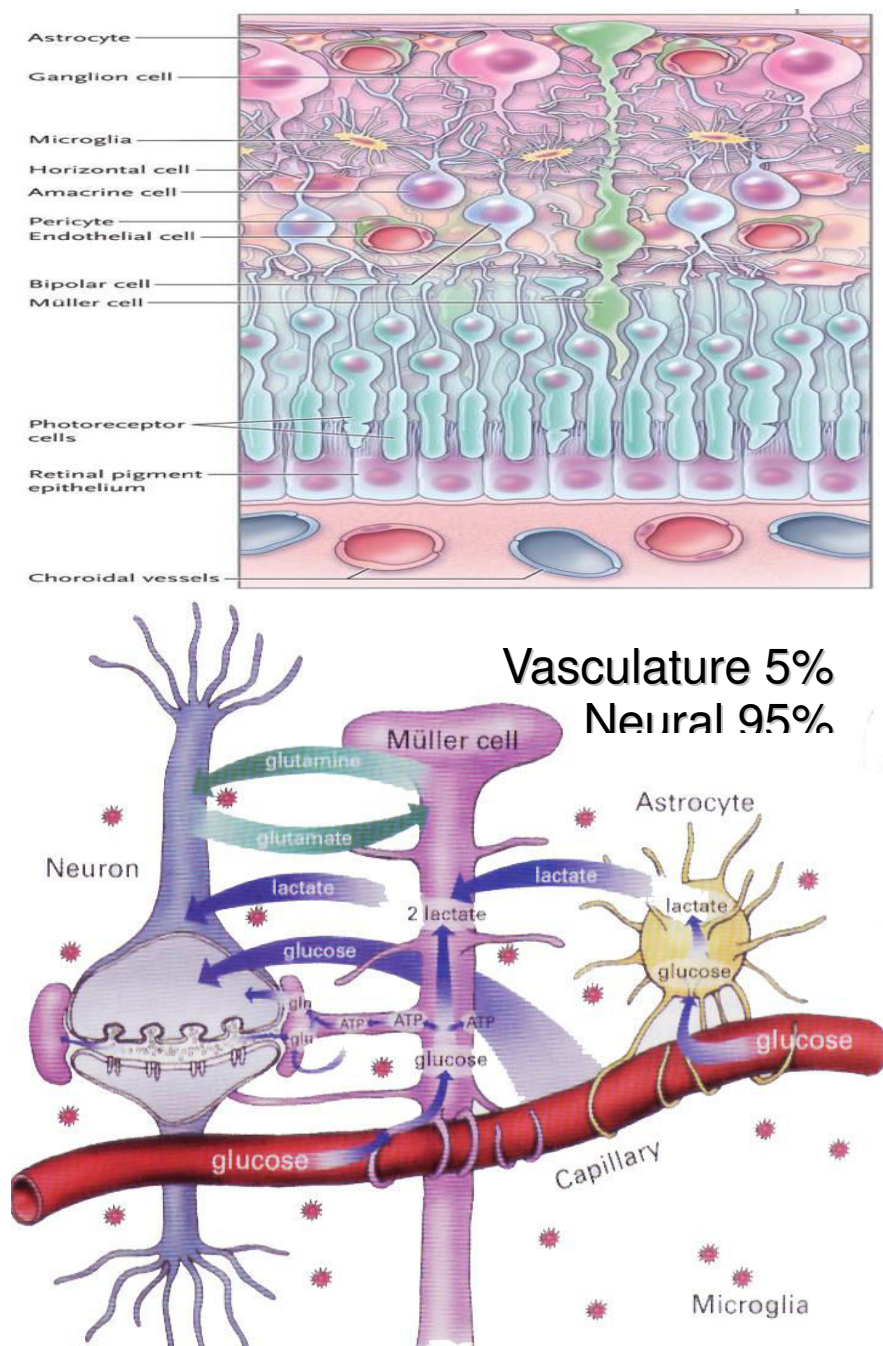


1.2.1 Natural history of diabetic retinopathy

DR is considered to be the result of changes in the retinal vasculature and the neuroretina.(Kohner 1993) The retina consists of 95% neural tissue and 5% vascular tissue (Figure 1.2.2).(Antonetti et al. 2012) It is primarily concerned with

the retinal capillaries and effects the entire neurosensory unit (which consists of astrocytes, Muller cells, amacrine and ganglion cells). Histologically, the earliest vascular changes are usually a decrease in the number of capillary pericytes and a thickening of the basement membrane. These occur long before any clinically visible lesions develop.

Figure 1.2.2: The neurovascular unit of the retina (Antonetti et al. 2012)

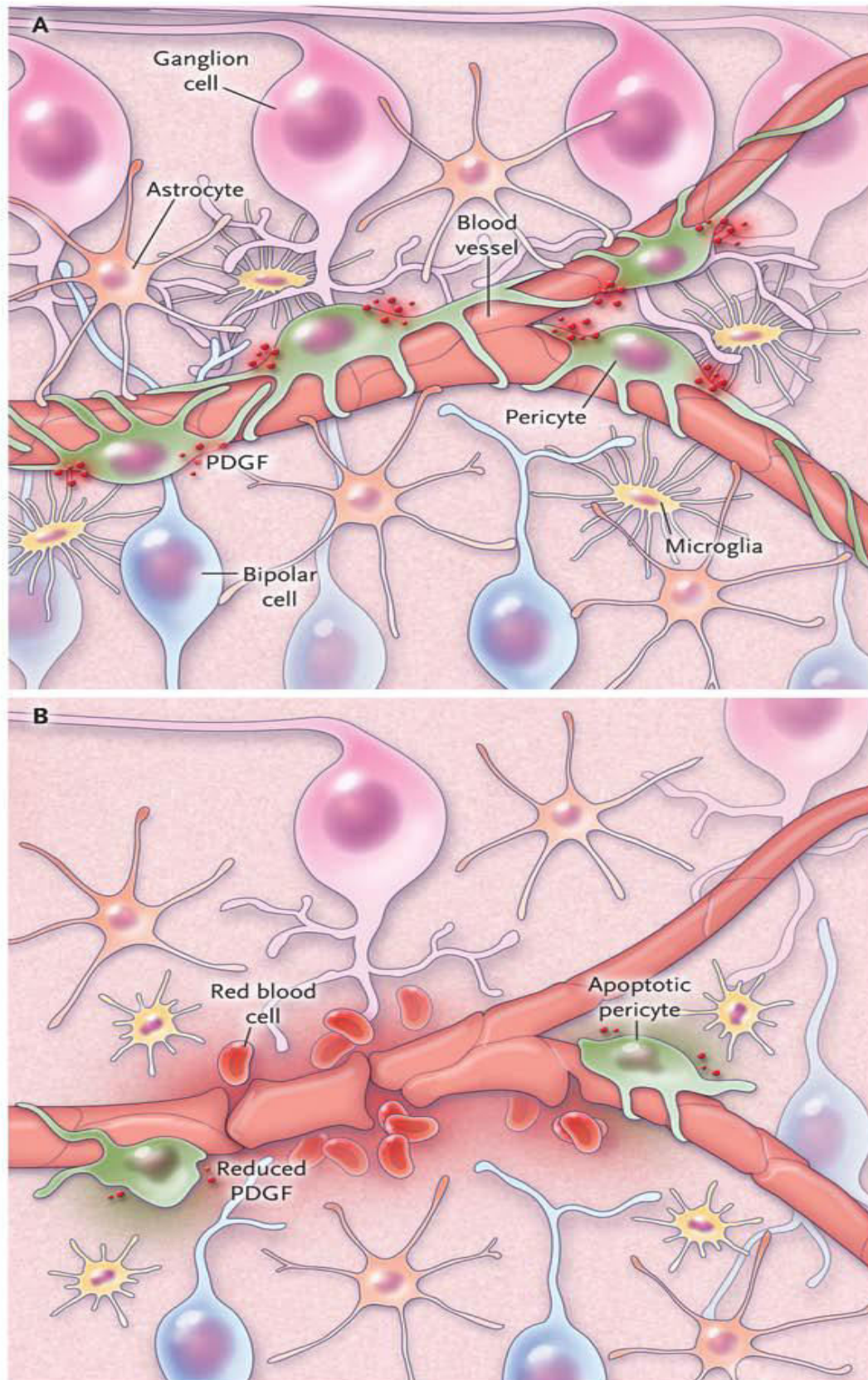


1.2.1.1 Neurovascular unit

Changes in the neuroretina may occur even before the onset of microvascular changes.(Lieth et al. 2000, Antonetti et al. 2006) Most retinal neurons and glial cells are altered and are progressively impaired with worsening DR. Figures 1.2.3A&B illustrates the disruption of the neurovascular unit due to diabetes. Additional alterations include biochemical defects, such as impaired control of glutamate metabolism, which is the major neurotransmitter,(Gowda et al. 2011) as well as loss of synaptic activity and dendrites,(Gastinger et al. 2008, VanGuilder et al. 2008) apoptosis of neurons primarily in the ganglion-cell and inner nuclear layers,(Barber et al. 1998) and activations of microglial cells that may protect the inner retina from injury but also contribute to the inflammatory response.(Zeng et al. 2008) These findings suggest that DR represents a sensory neuropathy that affects the retinal parenchyma, not dissimilar to peripheral diabetic neuropathy.(Cheung et al. 2010, Antonetti et al. 2012)

There is evidence that the disruption of the neuroretina caused by diabetes leads to changes in electroretinograms (ERG),(Lovasik et al. 1993) resulting in altered dark adaption (Henson et al. 1979) and reduced contrast and colour sensitivity.(Della Sala et al. 1985, Kurtenbach et al. 1994, Lieth et al. 2000, Kurtenbach et al. 2006) These changes have been shown to occur well before any first visible signs of DR. The relationship between the neural and vascular units of the retina in the pathogenesis of DR remains to be clarified. .(Antonetti et al. 2012) However, more recently the neurosensory retina can be observed by slit-lamp biomicroscopy and insight into the relationship between the retinal neurovascular unit could be achieved by the undertaking of a prospective assessment of diabetic patients using clinical and state-of-the-art functional and imaging technologies.

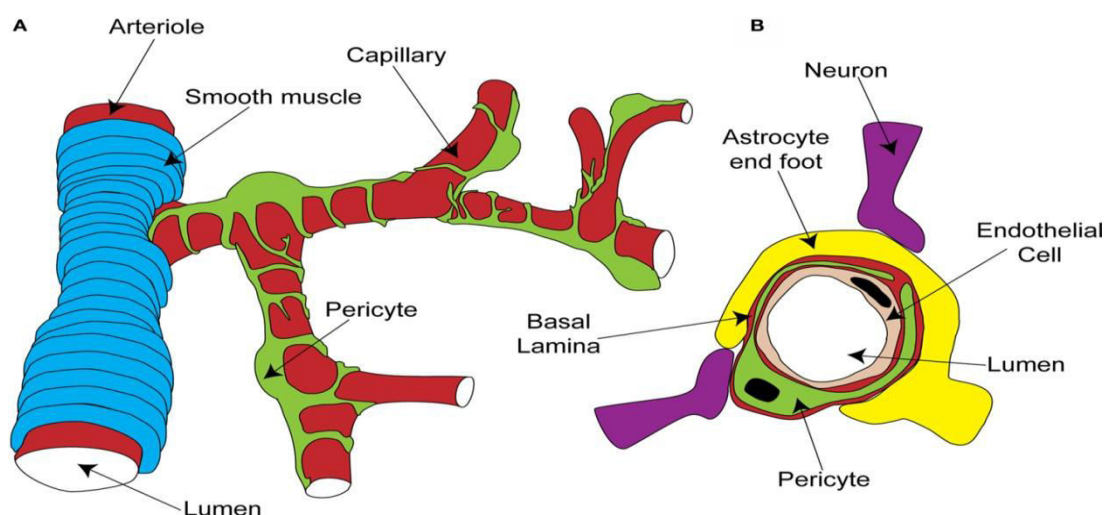
Figure 1.2.3: Retinal neurovascular Unit (Antonetti et al. 2012) A) normal, B) diabetes



1.2.2.2 Microvascular changes

Pericytes are an important constituent of the wall of retinal microvasculature with contractile properties to control vessel calibre and therefore blood flow. (Kohner 1993) Figure 1.2.4 shows the location of pericytes within capillaries. The loss of pericytes, creating ghost cells, are followed by the loss of capillary endothelial cells. Apoptosis, or programmed cell death, is thought to account for the disappearance of both cell types and is caused by hyperglycaemia due to variety of mechanisms e.g. Sorbitol etc. The loss of pericytes means the vessels become rigid, with increased blood flow,(Kohner 1993) the endothelium of the vessel wall is damaged by the increased shear stress. Destruction of the endothelial cells and increased basement membrane thickness, eventually leads to a breakdown of the blood-retina barrier, increasing the permeability of vessel walls to proteins and other substances. Thickening of the basement membrane is mainly a consequence of hyperglycaemia and/or a consequence of the accumulation of advanced glycosylation end products (AGEs).(Jennings 1992, Tooke 1992, Roy et al. 1994)

Figure 1.2.4: Location of pericytes within capillaries (Hamilton et al. 2010)



Form A) rings of smooth muscle encircle arterioles, while pericytes send processes along and around capillaries, without fully covering the vessel. B) Pericytes are located outside the endothelial cells and are separate from them and the parenchyma by a layer of basal lamina. In the parenchyma, astrocyte end-feet and neuronal terminals are closely associated with the capillary.(Hamilton et al. 2010)

Microaneurysms are the first feature of DR to become visible on clinical examination. Figures 1.2.5 and 1.2.6 show a trypsin digest of a microaneurysm and retinal image of microaneurysms respectively. However, even before these are clinically apparent, many more may be seen on fluorescein angiography accompanied by small areas of non-perfusion (Figures 1.2.6 and 1.2.7). The response to non-perfusion in some capillaries results in dilation of others and when this is localised (as most often occurs) a microaneurysm is formed (small dot lesion),(Kohner 1993) and are lined with endothelium which has increased permeability.

Figure 1.2.5: Trypsin digest images of the formation of a microaneurysm (Bernardino et al. 2006)

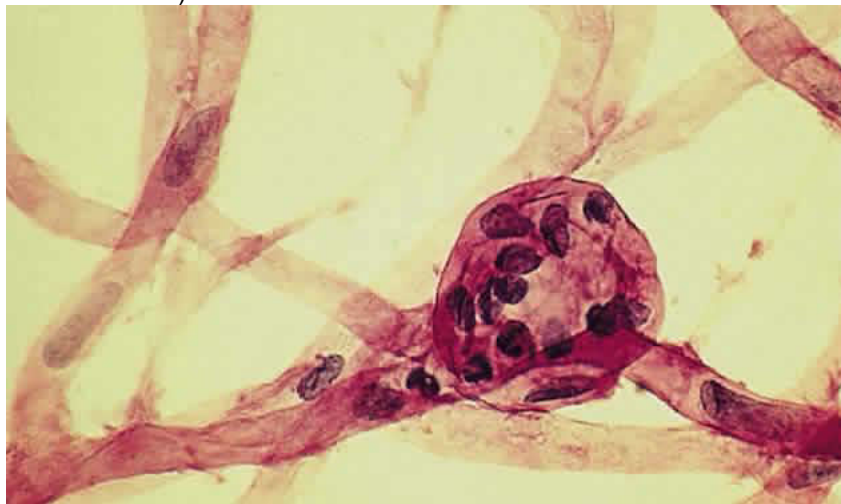


Figure 1.2.6: Retinal images showing microaneurysms on the retina (arrows) (www.itoozhiayurveda.in)

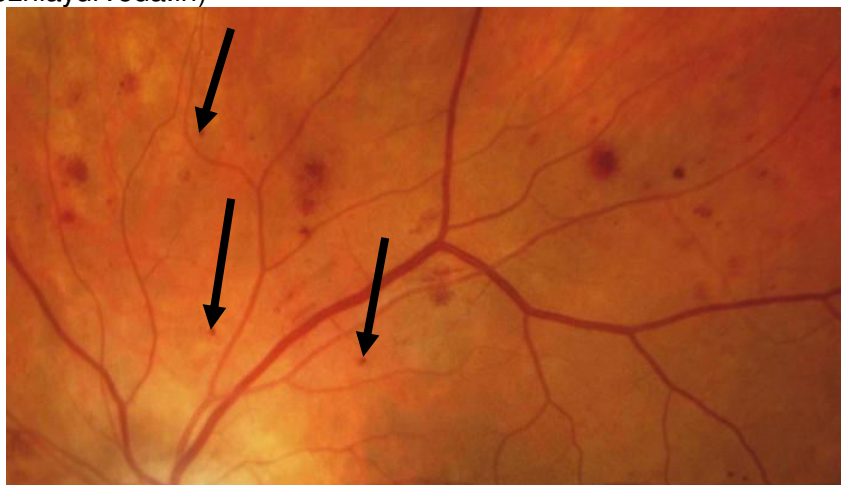
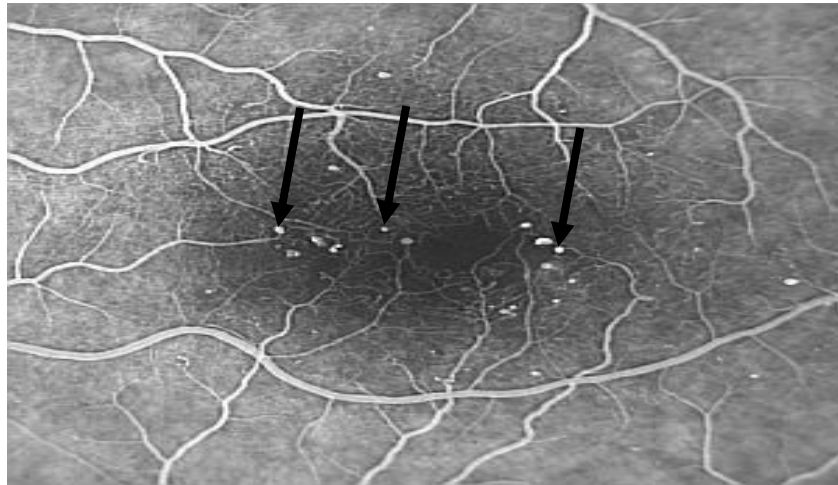


Figure 1.2.7: Fluorescein angiogram with microaneurysms fluorescing (Goatman 1997)



Increasing numbers of microaneurysms are often associated with retinal haemorrhages, which may be superficial and flame shaped, or deeper and more rounded lesions ('blot') and with small hard exudates, which are an accumulation of plasma lipoprotein.(Cunha-Vaz 2010) Large blot haemorrhages tend to form at the interface of the perfused and ischaemic areas of the retina (Figure 1.2.8 and 1.2.9).

Figure 1.2.8: Diagram of the location of the different types of retinal haemorrhages within the layers of the retina. Reproduced from (www.opthobook.com 2007)

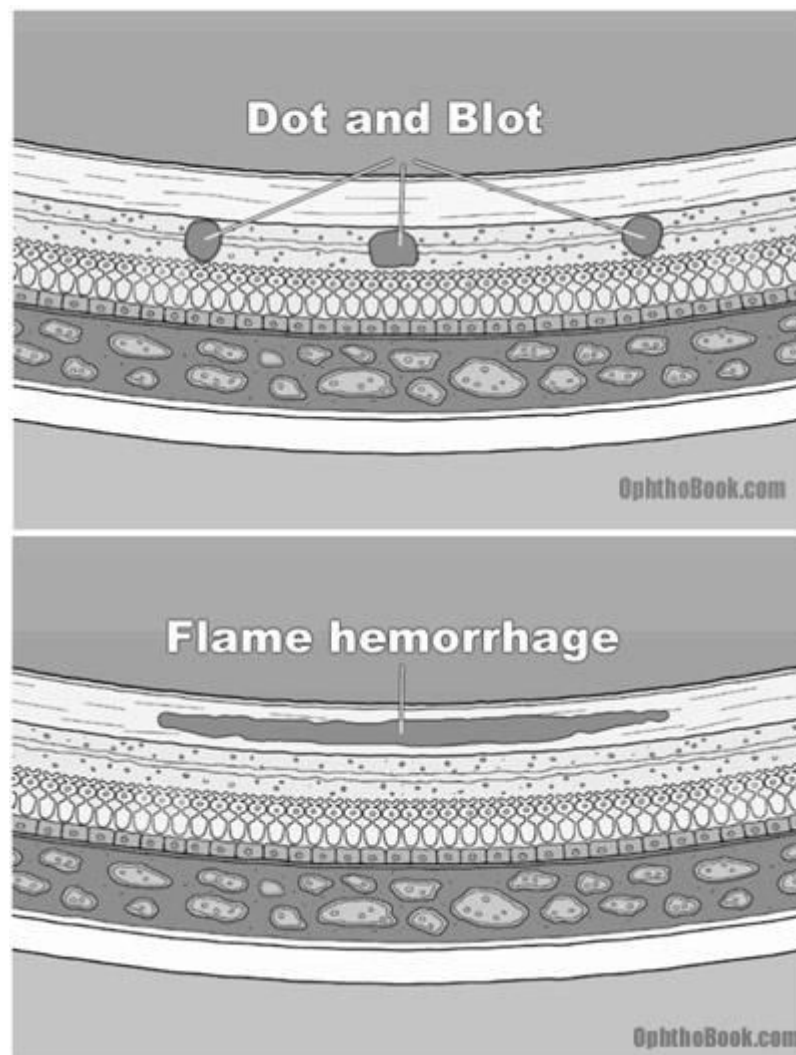
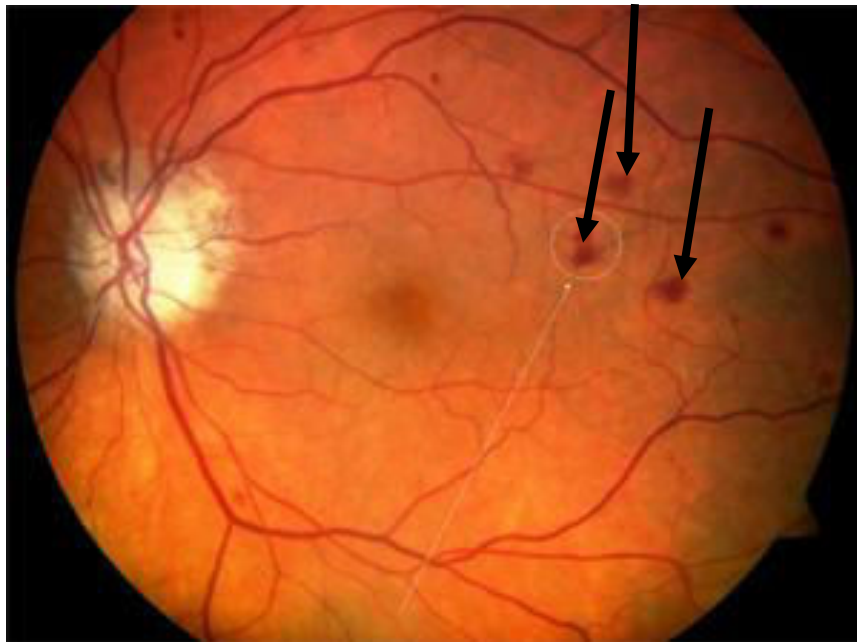
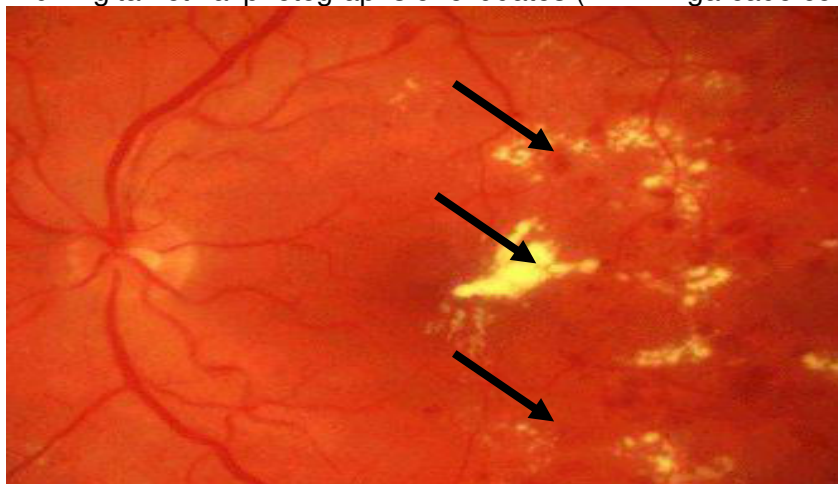


Figure 1.2.9: Retinal image showing retinal haemorrhages (www.joneseye.com 2013)



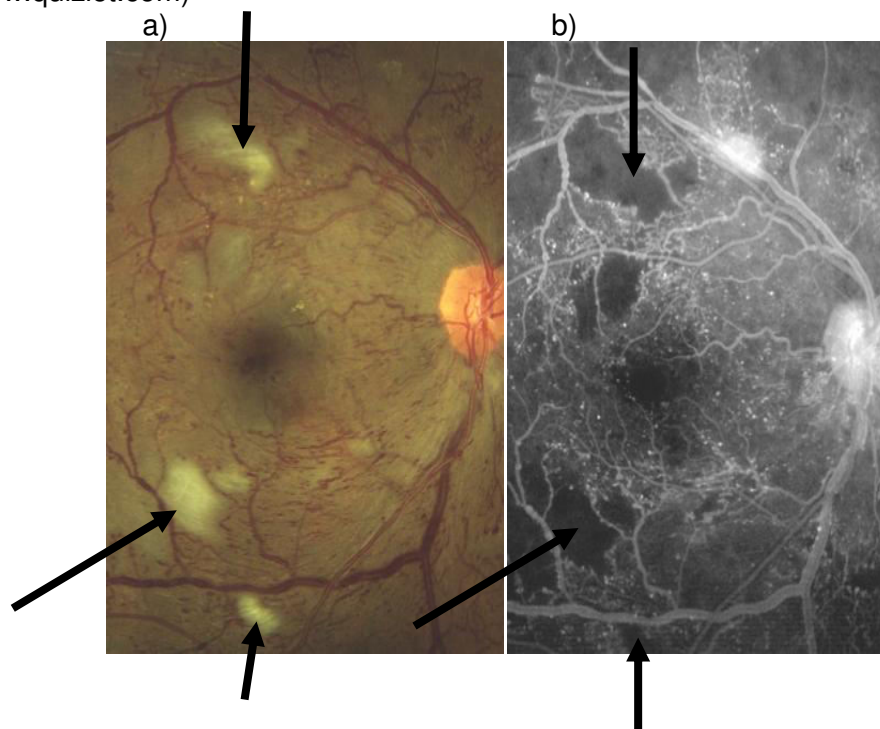
Exudates composed of lipid material develop and appear as yellow deposits often larger than the microaneurysms. They have a distinctive yellow shiny appearance (Figure 1.2.10). Their origin is thought to be leaky capillary blood vessels and microaneurysms in the retina. They may be transient and reabsorbed by the retina, though they tend to increase in total number over time.(Kohner 1991)

Figure 1.2.10: Digital retinal photographs of exudates (www.imgarcade.com)



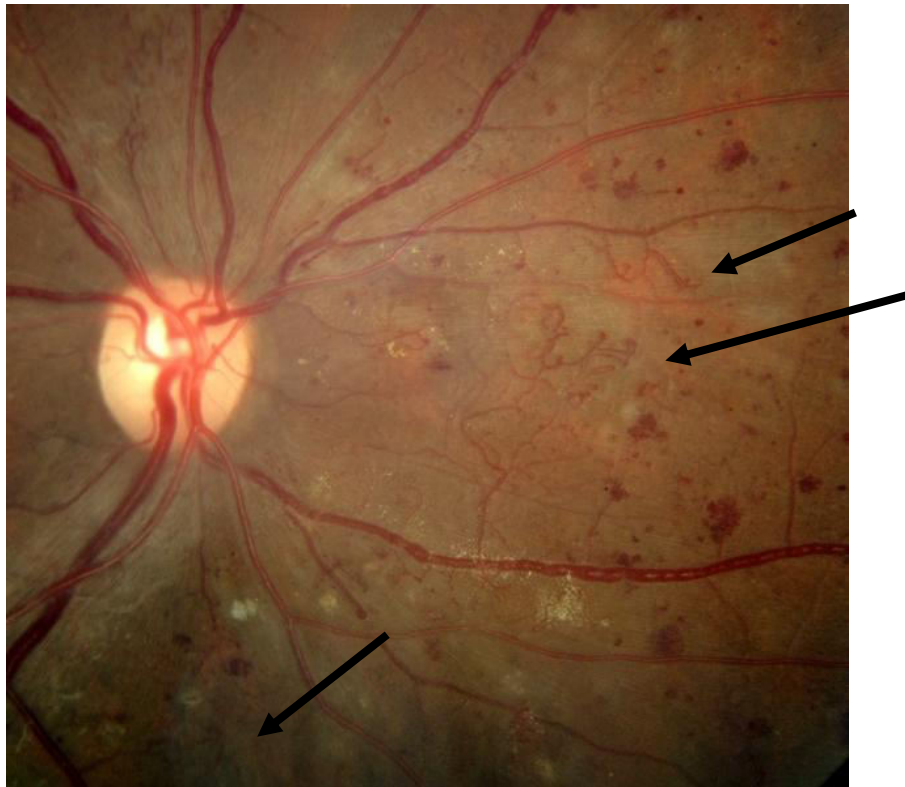
As ischaemia increases, the number of haemorrhages increase and evidence of focal ischaemia in the form of Cotton Wool Spots (CWS) may appear which are infarctions of the retinal nerve fibre layer (Figure 1.2.11).

Figure 1.2.11: Retinal images showing CWS a) digital image and b) a fluorescein angiogram of the same images showing the CWS as areas of non perfusion (www.quizlet.com)



CWS and haemorrhages may be present in ischaemic retinal conditions other than DR, but in the presence of microaneurysms are considered to be part of the process of DR.(Early Treatment Diabetic Retinopathy Study Research Group 1991c) Intra-Retinal Microvascular Abnormalities (IRMAs), i.e. dilation of the retinal capillary bed, can form in what appear to be avascular areas of the retina (Figure 1.2.12). These IRMAs may represent the earliest form of neovascularisation.(Early Treatment Diabetic Retinopathy Study Research Group 1991c)

Figure 1.2.12: Digital image depicting IRMA's



Abnormalities may also be observed in the larger blood vessels. The venules may develop segments which are dilated alternating with segments that are constricted resembling beading (Figure 1.2.13). Duplication of veins may also develop so that there appear to be parallel veins in some areas (reduplication) (Figure 1.2.14). (Early Treatment Diabetic Retinopathy Study Research Group 1991c)

Figure 1.2.13: Retinal image depicting venous beading (Hall 2011)



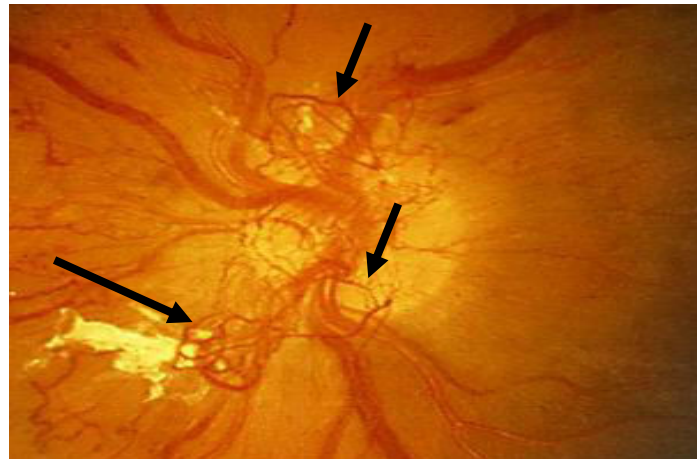
Figure 1.2.14: Close up retinal image showing venous loop/reduplication (www.imagebank.asrs.org)



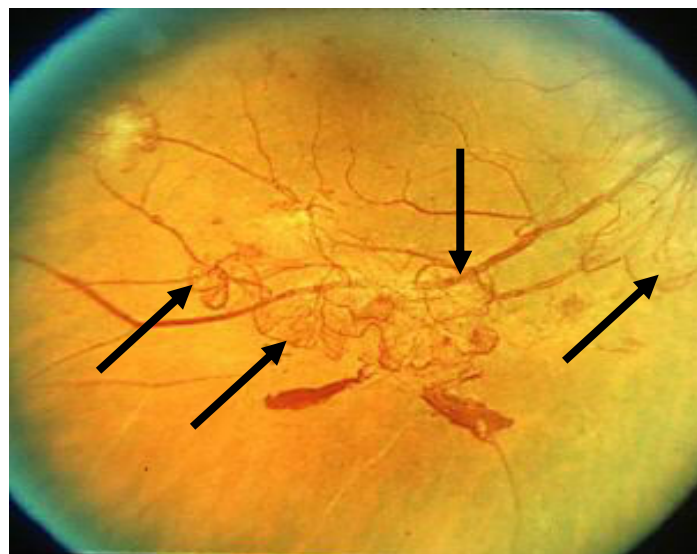
New vessels usually develop from the veins in the retinal periphery (new vessels elsewhere, NVE) or on the optic disc (new vessels on the disc, NVD) (Figure 1.2.15). The location of the new vessels determine the prognosis in terms of visual outcome.(Kohner 1991) When they occur at the disc, more than 50% of affected eyes may become blind within 5 years, compared with less than one third when new vessels are located away from the disc. They arise generally, although not exclusively when there are large areas of avascular retina in the vicinity. (Davis 1992) They later develop more characteristic frond-like patterns.

Figure 1.2.15: Growth of A) NVD(www.imagebank.asrs.org), B) NVE (www.eyecasualty.co.uk)

A)



B)



Evidence from the DRS showed that certain features of new vessels and vitreous and pre-retinal haemorrhage conferred a greater likelihood of severe visual loss if untreated.(Diabetic Retinopathy Study Research Group 1981a) These features were termed 'high risk characteristics' (HRCs) (Figure 1.2.16).

Figure 1.2.16: DRS high risk characteristics

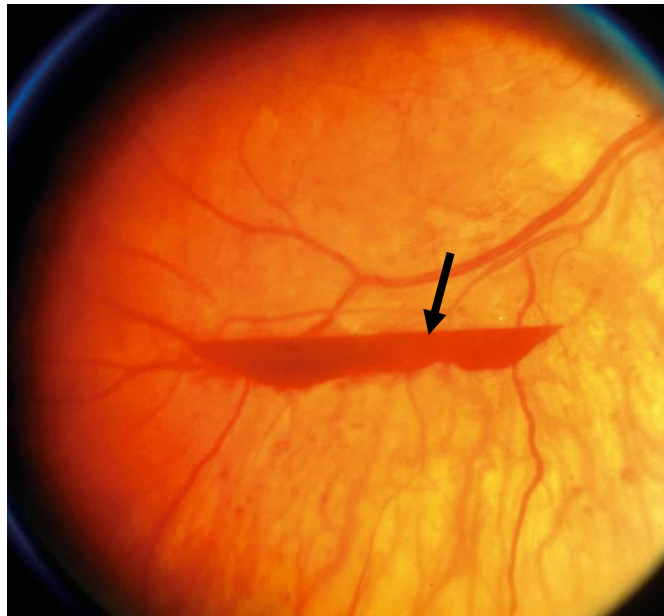
1. NVD > 25% of disc area, +/- Vitreous Haemorrhage, Pre-retinal Haemorrhage
2. NVD < 25% of disc area, + Vitreous Haemorrhage and/or Pre-retinal Haemorrhage
3. NVE > 50% disc area in size

The new vessels usually develop a fibrous sheath covering and break through the internal limiting membrane when they become attached to the posterior surface of the vitreous, which they use as a scaffold on which they continue to grow. The retracting vitreous often pulls on the vessels causing haemorrhage. The development and progression of DR maybe asymptomatic up to this stage (unless maculopathy has also developed), and symptoms only occur if these new vessels bleed causing vision to become obscured. The new vessels themselves do not cause any visual symptoms, it is the bleeding from the new vessels that are responsible for the visual loss.

Bleeding at this stage may initially produce 'boat shaped' haemorrhages if limited to the pre-retinal space (Figure 1.2.17), or vitreous haemorrhage with sudden visual loss if more generalised. Early vitreous haemorrhages may be small, with only transient visual loss, but may be an indication of impending major haemorrhage. Small haemorrhages may clear within a few weeks, but large ones may never clear, or do so very slowly.(Davis 1992) Without treatment, it has been demonstrated that

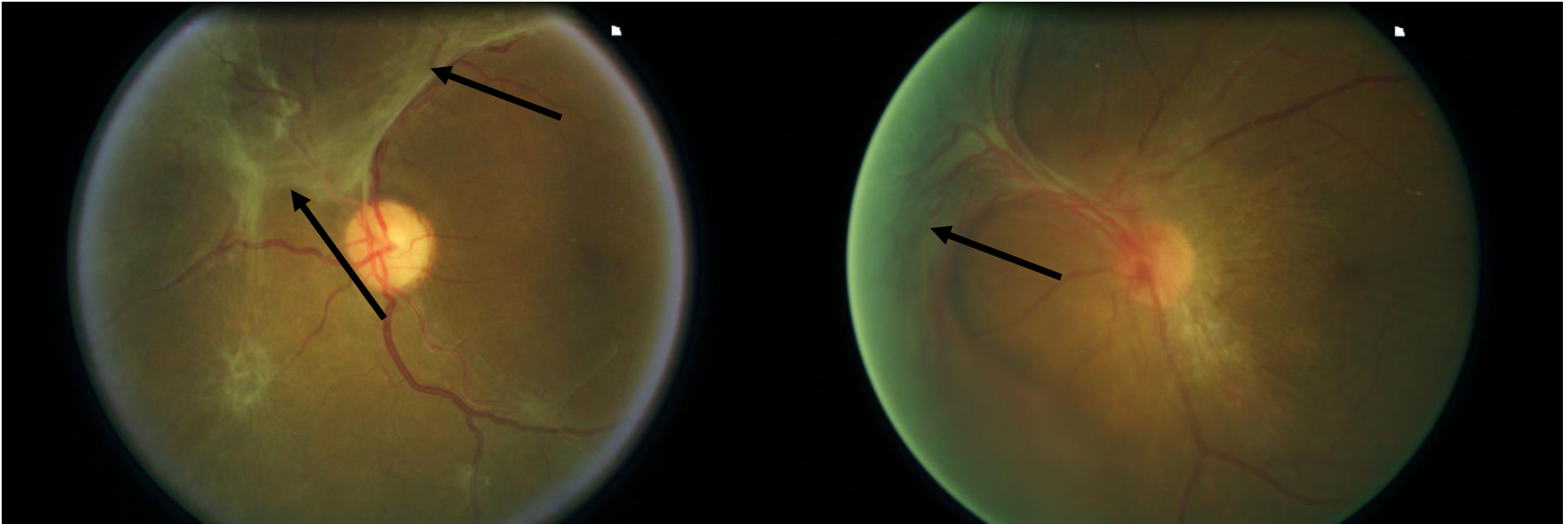
approximately one third of patients will be blind in both eyes within one year of their first vitreous haemorrhage, and only 14% of patients will have good vision within five years of developing new vessels.(Caird et al. 1968)

Figure 1.2.17: Pre-retinal haemorrhage (www.ucdenver.edu)



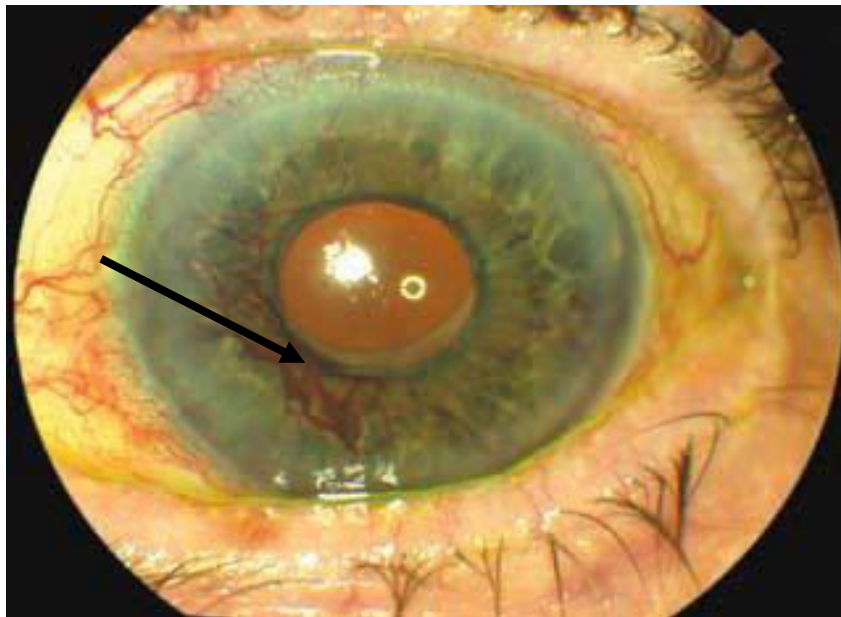
Fibrous tissue accompanying new vessels can exert traction on the retina, either due to its own contraction, or secondary to posterior vitreous detachment (Figure 1.2.18).(Davis 1992) Traction or retinal detachment normally involves the posterior pole and hence the macular area and will cause a decrease or distortion in vision. It is uncommon for spontaneous regression to occur at this stage. The visual loss related to these fibro-vascular abnormalities is usually sudden and unexpected

Figure 1.2.18: Fibrous tissue with traction



In some subjects, especially where ischaemia is a major feature, new vessels and fibrosis may also occur on the iris (rubeosis iridis), and in the angle of the anterior chamber (Figure 1.2.19). The resulting obstruction to normal drainage of aqueous fluid gives rise to painful glaucoma, which, if untreated, rapidly leads to blindness.(Kohner 1991)

Figure 1.2.19: Rubeosis iridis



1.2.1.4 Maculopathy

Diabetic maculopathy is defined as DR within one disc diameter (DD) of the centre of the fovea.(Chowdhury et al. 2002) There are two aspects of maculopathy, oedema where lipoproteins accumulate within the retina and ischaemia where there is a closure of perifoveal capillaries. Macular oedema may be focal or diffuse (Figure 1.2.20). Focal macular oedema is characterised by an increase in retinal thickening due to leakage from microaneurysms which are frequently associated with hard exudates.(Cunha-Vaz 2010) Diffuse macular oedema is caused by leakage from abnormally dilated capillaries, arterioles and venules in the macular area, and sometimes associated with cystic lesions, but with less visible focal

vascular damage and fewer hard exudates.(Chowdhury et al. 2002) Table 1.2.1 describes the principle features of each type of maculopathy.

Figure 1.2.20: Retinal images depicting the diabetic macular oedema A) Focal (Ober et al. 2009) B) Diffuse
A)



B)



Table 1.2.1 Categories of maculopathy

Oedematous	Focal	Localised areas of retinal thickening associated with focal leakage of individual microaneurysms or clusters of microaneurysms or dilated capillaries (Bhagat et al. 2009)
	Diffuse/cystoid	More generalised and chronic form of oedema, with widespread macular leakage and pooling of dye in cystic spaces (Bhagat et al. 2009)
Ischaemic	Ischaemic	Microaneurysms and haemorrhages with a small amount of capillary nonperfusion evident with fluorescein angiography. Varying oedema is present ranging from mild to cystoid in appearance.

Diabetic maculopathy may be central involving or non-central involving as well as tractional due to vitreo-retinal pathology or non-tractional (intraretinal). (The Royal College of Ophthalmologists 2012)

Maculopathy and the visual distortion and decreased visual acuity associated with oedema (clinically significant macular oedema [CSMO] is defined in Figure 1.2.21).

Maculopathy can occur in the presence of microaneurysms, haemorrhages, CWS, IRMA, and venous changes. (Klein et al. 2003) The associated visual loss is progressive. Without treatment about one third of affected eyes may be expected to become blind within five to seven years. (British Multicentre Study Group 1983, Early Treatment Diabetic Retinopathy Research Study Group 1985)

Figure 1.2.21: Definition of clinically significant macular oedema (Early Treatment Diabetic Retinopathy Research Study Group 1985):

- Retinal thickening within 500µm of the centre of the fovea
- Hard exudates within 500µm of the centre of the fovea with adjacent retinal thickening
- Retinal thickening 1DD or larger in size located within 1 DD of the fovea.

1.2.2 Classification of diabetic retinopathy

The need for a classification of DR, to allow the evaluation of treatment and natural progression was recognised long ago. Early classifications were disadvantaged by

the need for detailed and time consuming fundal drawings to complete a full evaluation.(Lee et al. 1966) The arrival of reliable retinal photography in 1955 facilitated the availability of standard photographs with which an individual's eyes could be compared. The Hammersmith classification was one of the first to use this method.(Oakley et al. 1967) Five types of lesion were recognised: microaneurysm and haemorrhage, exudate, new vessels, venous irregularities and proliferation. These lesions were graded on a scale from 1 to 5 depending on severity. Macular involvement was not identified separately and CWS were ignored. This initial classification was limited, but the use of standard photographs and lesion grading was firmly established.

The first internationally recognised classification of DR was established in 1968, i.e. the Airlie House classification.(Davis et al. 1969) Fifteen clinical features and two assessments one based on fluorescein angiography and one including seven standard colour photographs were each graded as 'absent' (0), 'mild to moderate' (1), and 'moderate to severe' (2). The features assessed in the Airlie classification are detailed in Table 1.2.2.

Table 1.2.2 : Features of the Airlie House classification of diabetic retinopathy

Grading category	Features
Non-proliferative	HM and/or MA EX 'Soft exudates' (CWS) Venous abnormalities Intraretinal microvascular abnormalities (IRMA) Retinal oedema at the macula
Findings on fluorescein angiography	Arteriovenous phase (15-25 seconds): IRMA and MA Late phase (3-5 minutes): Dye leakage
Proliferative	Neovascularisation within 1 disc diameter of disc Neovascularisation areas other than disc Fibrous proliferation within 1 disc diameter of disc Fibrous proliferation areas other than disc Plane of proliferation Retinal elevation
Vitreous haemorrhage	Pre-retinal haemorrhage Vitreous haemorrhage History of vitreous haemorrhage

HM - haemorrhage; MA - microaneurysm; EX - exudates; CWS - cotton wool spots;

An additional 3 standard photographs were made available for those wanting to further grade CWS, NVE and fibrous proliferation. Macular oedema was recognised as an important separate feature, though not linked to the presence of exudates.

Most subsequent classifications of DR have been adapted from the Airlie House classification. The first major modification was published in 1981 following evidence of the DRS study. (Diabetic Retinopathy Study Research Group 1981c, a) The needs of the Early Treatment Diabetic Retinopathy Study (ETDRS) Research Group

resulted in further expansion, with more emphasis being placed on early changes and lesions at and around the macula, particularly macular oedema.

However, the Airlie House and ETDRS classifications were overly complex, being designed to assess in detail the effectiveness of treatment for DR. However, this rendered them unwieldy as tools for the classification of DR in clinical practice. The principles of the DRS classification were used by the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) in a clinical grading system for assessing progression of DR in persons with type 1 diabetes in 1984.(Klein et al. 1984a) The patient's final DR grade was determined either as the DR level in the worst eye, or as the level in each eye, which proved to be more sensitive in detecting progression. An important feature of this study was the recognition that the presence of some lesions, particularly CWS and IRMA, conferred a higher risk of progression to PDR (50% and 61% respectively over six years compared all persons with type 1 diabetes of 44%).

Over the next 2 years, various amendments to this classification were published.(Klein et al. 1984a, Davis et al. 1985, Early Treatment Diabetic Retinopathy Study Research Group 1991b) The assessment of DR level for an individual evolved from being based on individual fields,(Klein et al. 1984a) through to assessment by 'worse eye only' or 'worse eye emphasised' to a 'median DR level' per subject in the KROC study.(Davis et al. 1985)

The completion of the ETDRS allowed a more detailed assessment of the severity of DR and risk of progression to PDR to be made, though risk factors for the development of macular oedema were not assessed.(Early Treatment Diabetic Retinopathy Study Research Group 1991c) The resulting ETDRS final DR severity scale provided 13 levels of severity per eye, based on seven field 30° stereoscopic

photographs. It was derived from the lesion-based interim ETDRS scale,(Early Treatment Diabetic Retinopathy Study Research Group 1991b) and incorporated the principles of both the WESDR and KROC systems, being numerically based with the grade of DR progressing from 10 (no retinopathy) to 85 (advanced vitreous haemorrhage). A summary of the ETDRS final grading scale is reproduced in Table 1.2.7.

Table 1.2.3 : ETDRS Final Retinopathy Severity Scale

Level	Severity	Definition
10	DR absent	MA and other characteristics absent
14	DR questionable	EX, CWS or IRMA definite; MA absent
15	DR questionable	HM definite; MA absent
20	Microaneurysms only	MA definite; other characteristics absent
35	Mild NPDR	Venous loops \geq D/1 CWS, IRMA, or VB = Q HM present EX \geq D/1 CWS \geq D/1
43	Moderate NPDR	HM/MA = M/4-5 or IRMA = D/1-3 (NOT both)
47	Moderately Severe NPDR	Both Level 43 characteristics and/or one (only) of the following: IRMA = D/4-5 HM/MA = S/2-3 VB = D/1
53	Severe NPDR	\geq 2 of the 3 level 47 characteristics HM/MA \geq S/4-5 IRMA \geq M/1 VB \geq D/2-3
61	Mild PDR	FPD or FPE present with NVD and NVE absent; or NVE = D
65	Moderate PDR	1) NVE \geq M/1 or NVD = D; and VH and PRH = A or Q 2) VH or PRH = D and NVE < M/1 and NVD absent
71	High Risk PDR	1) VH or PRH \geq M/1 2) NVE \geq M/1 and VH or PRH \geq D/1 3) NVD = D and VH or PRH \geq D/1 4) NVD \geq M
75	High risk PDR	NVD \geq M and VH or PRH \geq D/1
81	Advanced PDR: fundus partly obscured, centre of macula attached	NVD cannot grade, or NVD < D and NVE = cannot grade in \geq 1 field and absent in all others; and retinal detachment at centre of macula < D
85	Advanced PDR: posterior fundus obscured or centre of macula detached	VH = VS in fields 1 and 2; or retinal detachment at centre of macula = D
90	Ungradeable even as levels 81 or 85	

Notes:

Levels 14 and 15 are not considered separate steps, but pooled with level 10 or 20

Levels 35 and above require the presence of MA.

Abbreviations:

DR = Diabetic retinopathy; NPDR = Non-proliferative DR; PDR = proliferative DR; MA = Microaneurysm; HM = Haemorrhage; EX = Hard Exudate; CWS = Cotton wool spot (soft exudate); IRMA = Intraretinal Microvascular abnormality; VB = venous beading; FPD = fibrous proliferations at disc; FPE = fibrous proliferations elsewhere; NVD = New vessels at the disc; NVE = New vessels elsewhere (> 1 disc diameter from disc); VH = vitreous haemorrhage; PRH = preretinal haemorrhage.

Severity Grades:

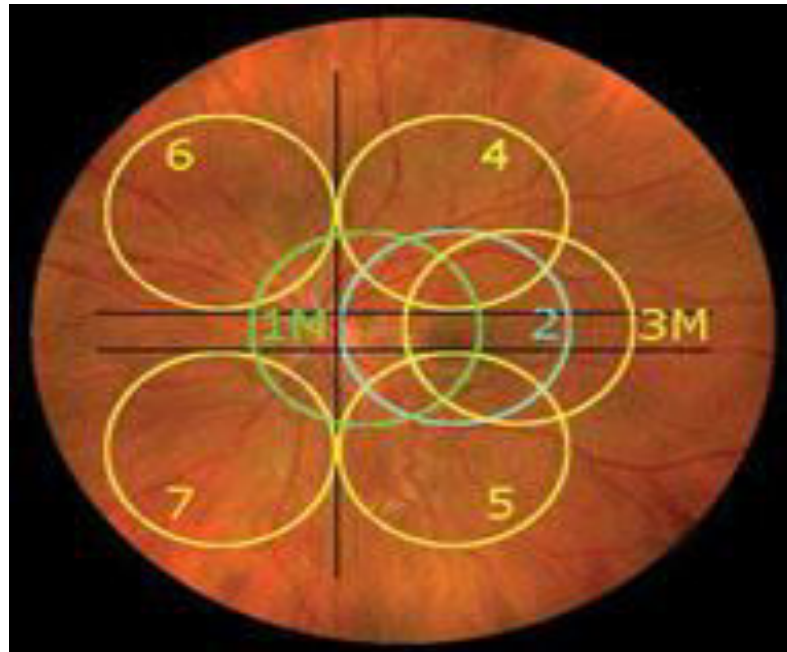
Q = Questionable; D = Definite; M = Moderate; S = Severe; VS = Very severe.

Number of fields (out of 7) in which lesions appear follow after '/'.

Examples: CWS ≥ M/2-3 means Soft exudates of equal to or greater than moderate severity compared with standard photographs present in 2 to 3 fields; VB = Q means venous beading questionable.

As well as the classification of DR being updated following evidence from clinical trials and population studies, the number of fields required for the assessment of DR were also assessed. The WESDR group recognised that seven field stereo photography was time consuming and not always possible in routine clinical practice, and assessed the sensitivity of employing fewer 30° fields in 1989.(Moss et al. 1989) Use of standard fields one and two (macular centre and nasal) gave an agreement of 80% in determining all eight levels of DR (Figure 1.2.22). If the eight levels were reduced to 4, corresponding with no DR (level 10), mild non proliferative DR (NPDR) (levels 15 -20), moderate to severe NPDR (levels 30 -40) and PDR (levels 60 -70), agreement was 85% for standard fields one and two. The addition of two further fields (three and four, or four and five) increased agreement up to 91% for eight levels of DR and 95% for four levels. Addition of temporal fields (three and four) increased particularly the detection of new vessels, vitreous haemorrhage and pre-retinal haemorrhage.

Figure 1.2.22: Seven standard retinal fields (www.revophth.com)



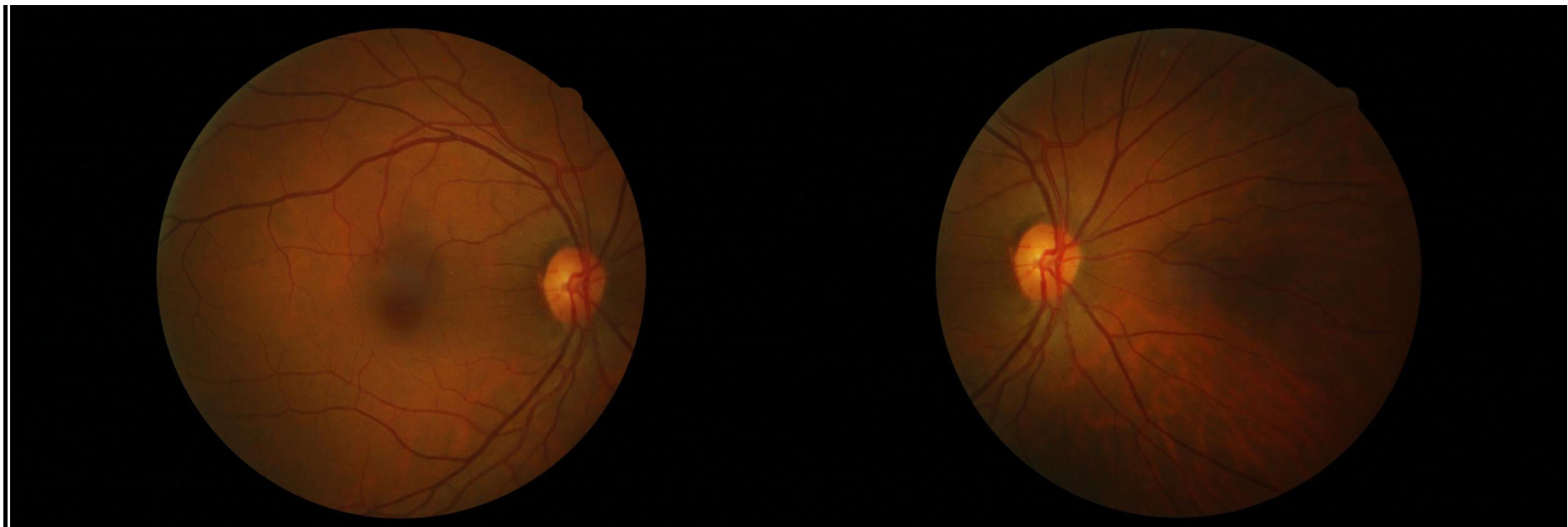
Area 1 corresponds to a disc centred image; Area 2 - macular centred; Area 3 - Macular centred; Area 4 - Superior temporal; Area 5 - inferior temporal; Area 6 - superior nasal; Area 7 - inferior temporal

The use of fewer standard fields was a feature of the epidemiology and prevention of diabetes (EURODIAB) study of complications in persons with type 1 diabetes.(Stephenson et al. 1994) This study used a grading system based on two 45° field colour retinal transparencies.(Aldington et al. 1995) The macular centred field was positioned so that the centre of the optic disc was at the nasal end of the horizontal meridian of the field of view, and the nasal/disc field positioned so that the medial edge of the optic disc was 1 disc diameter (DD) in from the temporal edge of the field on the horizontal meridian (Figure 1.2.23).

Figure 1.2.23: Two standard retinal fields A) macular centred and B) nasal

A)

B)



This gave access to an area of retina of approximately 80° horizontally and 45° vertically. In comparison, the seven standard retinal fields obtained with the 30° retinal camera provide a field of view of approximately 75° horizontally and 70° vertically, with more emphasis on the area temporal to the macula, and also the inferior and superior nasal areas. The total area of retina covered by the two 45° fields approximates to that obtained by four 30° fields because of variations in overlap. The EURODIAB grading system based on lesion counts and comparison with standard photographs. Lesion counts were then translated into a 6 level grading system detailed in table 1.2.4

Table 1.2.4 : EURODIAB retinopathy grading system

Level	Retinopathy features
Level 0	<u>No Retinopathy</u>
Level 1	<u>Minimal non-proliferative retinopathy:</u> HM/MA = grade 2-3 in 1 or 2 fields and/or EX grade 2-4 in 1 or 2 fields
Level 2	<u>Moderate non-proliferative retinopathy:</u> HM/MA grade 4 in only 1 field, <u>OR</u> HM/MA grade 2-3 in 1 or 2 fields <u>PLUS:</u> CWS grade 2-3 in 1 or 2 fields and/or IRMA grade 2 in 1 or 2 fields and/or VB grade 2 in 1 or 2 fields
Level 3	<u>Severe non-proliferative retinopathy (pre-proliferative):</u> HM/MA grade 4 in both fields, <u>OR</u> HM/MA grade 2-4 in 1 or 2 fields <u>PLUS:</u> CWS grade 4 in 1 or 2 fields and/or IRMA grade 2 in 1 or 2 fields and/or VB grade 3 in 1 or 2 fields
Level 4	<u>Photocoagulated:</u> Scars of photocoagulation in any field
Level 5	<u>Proliferative retinopathy:</u> ANY OF: NVD, NVE, Fibrous proliferation, disc or elsewhere Pre-retinal haemorrhage Vitreous haemorrhage

HM - haemorrhage; MA - microaneurysm; CWS - cotton wool spot; IRMA - intra-retinal microvascular anomaly; VB - venous beading; NVD - New vessels on the optic disc; NVE - new vessels elsewhere; EX - exudates

1.2.4.1 Classification of diabetic retinopathy for the purpose of screening

For use in a clinical, rather than a research setting, the EURODIAB classification was used to define a set of recommendations for screening for DR.(Kohner et al. 1990) These were agreed by members of a working party on DR, held at the Hammersmith Hospital in London in 1990 under the auspices of the St. Vincent declaration. These clinical categories are detailed in Table 1.2.5.

This latter system was used to derive the grading system used by the Welsh Community study of DR (WCSDR).(Gibbins 1999) This was then later further modified and used in the first pilot regional screening programme in Wales, the Bro-Taf DR Service (Bro-Taf DRS),(Bouhaimed et al. 2008) and in the beginning of the Welsh National screening programme - Diabetic Retinopathy Screening Service for Wales (DRSSW). A further revision was made in 2005 in conjunction with the All Wales Ophthalmology Group to provide the current grading system employed by the DRSSW. Table 1.2.6 details the changes that occurred from WCSDR to the Bro-Taf DRS and finally the DRSSW grading systems. All grading systems for DR recognise that the presence and quantity of certain features may confer a greater degree of risk of progression of disease, and are intended to allow appropriate classification, permitting timely intervention in order to prevent visual loss.

Table 1.2.5 : European field guide book screening categories and recommendations

For review in screening clinic in 6 -12 months:	
Mild Non-proliferative retinopathy:	<ul style="list-style-type: none"> - CWS in small numbers not associated with pre-proliferative lesions. - Occasional haemorrhages and/or microaneurysms and hard exudates not within 1 disc diameter of the macular area. - Drusen may sometimes be confused with hard exudates. Drusen, if not associated with other signs of age related macular degeneration, are not considered important.
Lesions to be referred as soon as possible for assessment by an ophthalmologist:	
Non-proliferative retinopathy without macular involvement:	- Large circinate or plaque hard exudates within the major temporal vascular arcades.
Non-proliferative retinopathy with macular involvement:	<ul style="list-style-type: none"> - Reduced visual acuity not corrected by pinhole (suggestive of macular oedema) - Haemorrhages and/or hard exudates within one disc diameter of the macula, with or without visual loss
Pre-proliferative retinopathy:	<ul style="list-style-type: none"> - Venous irregularities (beading, reduplication, loops), - and/or multiple haemorrhages - and/or multiple CWS - and/or intraretinal microvascular abnormalities
Sight threatening retinopathy, requiring immediate referral:	
Proliferative retinopathy:	<ul style="list-style-type: none"> - New vessels on the optic disc or elsewhere in the retina - Preretinal haemorrhage - Fibrous tissue
Advanced diabetic eye disease:	<ul style="list-style-type: none"> - Vitreous haemorrhage - and/or fibrous tissue - and/or recent retinal detachment - and/or rubeosis iridis
CWS - cotton wool spots	

Table 1.2.6: Comparison of the WCDRS, Bro Taff DRS and DRSSW standard grading protocols.

WCDRS grading		Bro-Taf DRS grading		DRSSW grading	
0	NoDR	0	No DR	R0	No DR
1	Non- PDR (mild) Occasional Hms and/or Mas Hard exudate not within 1dd of macular centre 1 CWS not associated with PPDR lesions	1	Minimal NPDR ≤ 5 Mas > 1 DD from fovea and/or 1 Hm > 1 DD from fovea	R1.1	Mild BDR < 5 Mas > 1 DD from fovea < 4 Hms > 1 DD from fovea 3 Mas < 1 DD from fovea ≤ 3 MA < 1 DD from fovea with VA better than 6/12 exudates > 2 DD from fovea \pm CWS (< 5)
2a	Non-PDR (moderate) without macular involvement Large Circinate or plaque hard exudates within temporal arcades but not < 1 DD from macula centre	2a	Mild NPDR > 5 Mas ≤ 2 Ma < 1 DD from fovea and/or ≥ 2 Hm > 1 DD from fovea and/or Ex outside arcades and/or ≤ 5 CWS Questionable IRMA	R1.2	Moderate BDR ≥ 5 Mas > 1 DD from fovea $\geq 4 < 8$ HMs > 1 DD from fovea > 3 Mas < 1 DD from fovea with VA $> 6/12$ Circinate or grouped exudates > 2 DD from fovea but within arcades Questionable IRMA <i>only in the presence of MA/HM</i>
2b	Non-PDR (moderate) with macular involvement Hm and/or hard exudates within temporal arcades < 1 DD from macula centre	2b	Mild NPDR Features of 2a and > 2 Ma < 1 DD from fovea and/or Ex within arcade > 1 DD from fovea		
		2c	Mild NPDR Circinate Ex within arcade > 1 DD from fovea		
3	PPDR Venous irregularities And/or multiple Hms And/or CWS And/or IRMA	3a	Moderate NPDR > 5 CWS Multiple Hm	R2	Severe BDR (PPDR) ≥ 8 blot haemorrhages <i>per eye</i> (superior and inferior hemi-fields) Venous irregularities, beading, reduplication, venous loops (but not on their own) Definite IRMA \pm CWS (but not CWS on their own)
		3b	Severe NPDR Venous irregularities (beading, loops, reduplication) Definite IRMA		
4	PDR New Vessels on disc or elsewhere Pre-retinal Hm	4	PDR New vessels on disc (NVD) and/or New vessels elsewhere (NVE) and/or	R3	PDR/ADED New vessels on disc (NVD) New vessels elsewhere (NVE)

WCDRS grading		Bro-Taf DRS grading		DRSSW grading	
	And/or fibrous tissue		Pre-retinal Hm and/or Fibrous tissue		Pre-retinal haemorrhage Vitreous haemorrhage Pre-retinal fibrosis Traction retinal detachment
5	Advanced diabetic eye disease Vitreous Hm And/or fibrous tissue And/or retinal detachment And/or rubeosis iridis	5	Advanced diabetic eye disease Vitreous Hm and/or Fibrosis/Traction and/or Retinal detachment (recent)		
6	Presence of photocoagulation from previous treatment				
7	Findings that observer finds difficult to interpret with reasonable certainty				
		Maculopathy		Maculopathy	
		M1	Hm < 1DD from fovea and/or Ex < 1 DD from fovea	MO	No Maculopathy
		M2	Possible CSMO (VA < 6/12)	M1	Possible Maculopathy Exudates < 2 DD >1DD from fovea > 3 Mas <1 DD from fovea with VA < 6/12 Hm < 2DD from fovea
				M2	Definite Maculopathy Exudates < 1 DD from fovea Retinal thickness changes < 1 DD from

Table 1.2.6 continued

Hm - haemorrhage; Ma - microaneurysm; Ex - exudate; CSMO - clinically significant macular oedema; DD - disc diameter; VA - visual acuity; NVE - new vessels on elsewhere; NVD - new vessels on the optic disc; BDR - background diabetic retinopathy; PPDR - pre-proliferative diabetic retinopathy; proliferative diabetic retinopathy; CWS - cotton wool spots; IRMA - intra-retinal microvascular abnormality

1.3 Epidemiology of diabetic retinopathy

It has been known for some time that estimates of prevalence and incidence of DR differ between type 1 and type 2 diabetes and that they are dependent on duration of diabetes and glycaemic control along with other risk factors including hypertension and dyslipidaemia.(Bodansky et al. 1982, Klein et al. 1985)

Historically they also vary between different time periods of data collection, due to changes in classification of both diabetes and DR, and different methods of detection of DR employed such as ophthalmoscopy direct/indirect, biomicroscopy, fluorescein angiography and photography using Polaroid, 35mm film or digital images. When comparing prevalence and incidence estimates hospital based clinic vs. community difference should also be taken into account. Community based programmes, such as DR screening in the UK, may underestimate the prevalence of sight-threatening DR due to the exclusion of persons who are under the care of a hospital eye service for DR reasons and therefore not subjected to screening. In contrast hospital based (ophthalmology) clinics may over-estimate the prevalence of sight-threatening DR for a particular population.

1.3.1 Prevalence and incidence of diabetic retinopathy

Prevalence is a measure of the frequency of disease within a population at a particular time. Whereas, incidence is defined as the number of new cases of a disease occurring over a defined period of time.

Much of the data regarding the prevalence and incidence of DR originates from the WESDR.(Klein et al. 1984b, c) In this extensive study, a large group of persons with diabetes living in South Wisconsin, USA were followed for more than 25 years. The subjects were divided into two groups; those with an age at diagnosis of diabetes less than 30 years (younger onset group), taken to be almost exclusively

persons with type 1 diabetes (n=996), and those with an age at diagnosis of 30 years or more (older onset group), predominantly persons with type 2 diabetes (n=1,370). The latter group were subdivided into those taking insulin (n=674) and those on other forms of treatment such as diet with or without oral hypoglycaemic agents (OHAs) (n=696). DR assessment was based on the ETDRS adaption of the Airlie House grading system,(Early Treatment Diabetic Retinopathy Study Research Group 1991b) with seven standard stereoscopic colour fundus photographs taken per eye following mydriasis.

The prevalence of any DR in the younger onset group was 71%,(Klein et al. 1984b) and in the older onset group using insulin was similar at 70%, whilst in those not using insulin the prevalence was 39%.(Klein et al. 1984c) In the younger onset group 23% had PDR,(Klein et al. 1984b) and in the older onset group those using insulin PDR occurred in 14%, and those not using insulin PDR was present in 3%.(Klein et al. 1984c) Macular oedema occurred in 6% of the younger onset group,(Klein et al. 1984b) 11% of the older onset group using insulin and 4% in those not using insulin.(Klein et al. 1984c) The data suggested a link between the types of diabetes and the severity of DR seen, with PDR more prevalent in the younger onset or type 1 group and macular oedema in the older onset or type 2 group.

In the WESDR the overall incidence of any DR was 40.3% over a four year period.(Klein et al. 2003) In the younger onset group the 4 year cumulative incidence of any DR was 59.0%,(Klein et al. 1989b) and for the older onset group was 47.4% in those using insulin and 34.4% in those not using insulin.(Klein et al. 1989a) Further follow up of the younger onset group indicated that almost all developed any DR after 14 years and the cumulative incidence of PDR was 37.0%.(Klein et al. 1998) The ten year incidence of macular oedema was 20.1% for

the younger onset group and 25.4% for older onset group on insulin therapy and 13.9% in those not using insulin.(Klein et al. 1995) Comparative figures for CSMO were 13.6%, 17.6% and 9.2% respectively. Since this landmark epidemiologic study, changes in the classification of diabetes and DR and the advances made in diabetes treatment may mean that these prevalence and incidence rates may not be relevant today.(Klein et al. 2009, Wong et al. 2009)

A systematic review carried out in 2004 identified a total of 153 publication reporting prevalence data and 70 providing incidence figures for DR, PDR and maculopathy in type 1, type 2 diabetes or mixed cohorts.(Williams et al. 2004) The overall prevalence estimates for DR reported were very broad ranging from 0-84.0% in persons with type 1 diabetes in the USA, 33.6-36.7% in the UK, and 10.8-68.3% in Scandinavian countries. In persons with type 2 diabetes the prevalence estimates for DR ranged from 7-55.0% in the USA, 21.0-52.0% in the UK and 18.8-65.9% in Scandinavia. The incidence of DR in persons with type 1 diabetes ranged from 33.0% to 89.3% over 2 and 10 years respectively in the USA, and 9.0%-56.0% over 5 and 7 years respectively in Europe. For type 2 diabetes it was 66.9% over 10 years in USA, and 22.0% over 6 years in the UK.

A more recent systematic review performed a pooled individual participant meta-analysis from 35 studies with a total of 22,898 participants, utilising retinal photographs with the aim of providing worldwide estimates for the prevalence of DR.(Yau et al. 2012) They estimated the prevalence of any DR at 77.0% and 32.0% in type 1 and type 2 diabetes aged 20-79 years, respectively. In type 1 diabetes the prevalence of PDR was 32.0% and for maculopathy 3.0% compared to 14.0% and 6.0% for type 2 diabetes respectively. These estimates were reasonably similar to those recorded earlier for the WESDR.(Klein et al. 1984b, c)

Both the prevalence and incidence of DR are influenced not only by type of diabetes but also duration of diabetes, glycaemic and blood pressure control, dyslipidaemia, the use of insulin, and possibly by ethnicity as well as other factors such as age, gender, pregnancy and genetic makeup.(Stewart et al. 1993)

1.3.2 Putative risk factors for diabetic retinopathy

1.3.2.1 Duration of diabetes

In almost all epidemiologic studies of DR the duration of diabetes is the most important characteristic associated with increased risk. Although not a causal factor in a way that is informative about the disease mechanisms itself, nevertheless it is an important consistent feature of most chronic complications seen in people with diabetes.(Klein et al. 2003) After 20 years of diabetes 80% of persons with type 1 diabetes will have developed DR and 50% sight-threatening DR. Whereas in persons with type 2 diabetes 50% will develop DR and 10% sight-threatening DR. Figure 1.3.1 shows how the prevalence of any DR and PDR and Figure 1.3.2 how CSMO increased with increasing duration of diabetes in the WESDR study.(Klein et al. 1984b, c)

Figure 1.3.1: Prevalence of any DR and PDR (Klein et al. 1984b, c)

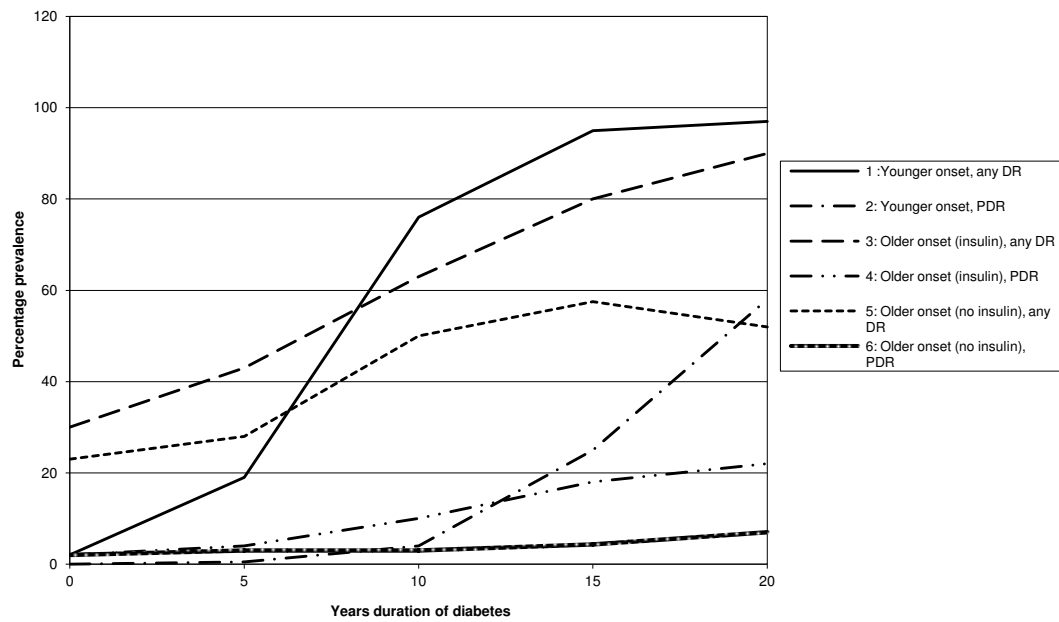
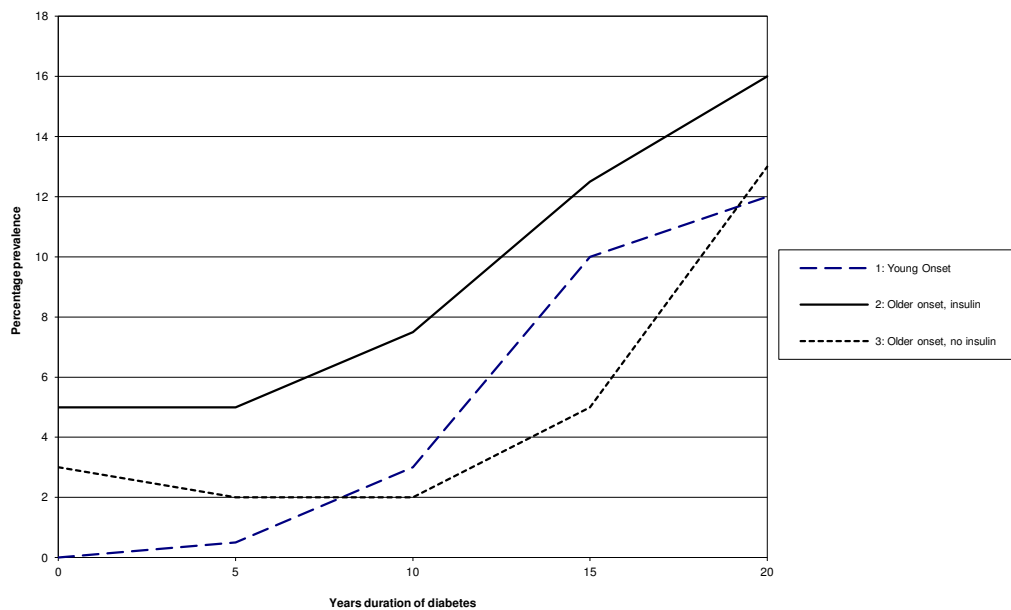


Figure 1.3.2: Prevalence of CSMO (Klein et al. 1984b, c)



The strength and time course of this relationship differs between those subjects with type 1 and type 2 diabetes. However, duration of disease in type 2 diabetes is often inaccurate due to the asymptomatic nature of the disease early on, therefore the exact age at onset is often unknown leaving the time course difficult to estimate in

this group.(Klein et al. 2003) Two studies have estimated, using the presence and severity of DR as a marker, that the onset of diabetes in those with type 2 diabetes may occur between four and seven years prior to diagnosis.(Harris et al. 1992, Porta M et al. 2014)

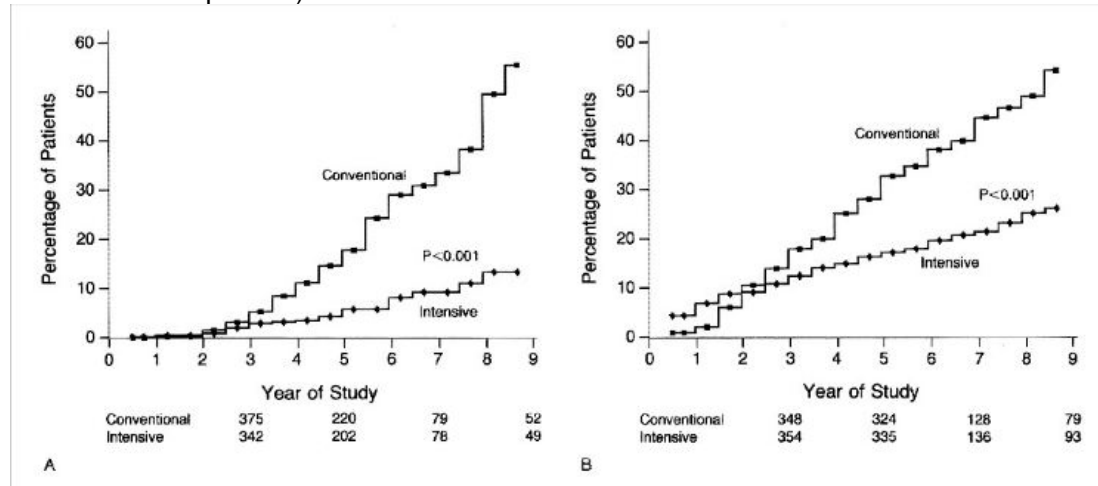
1.3.2.2 Glycaemic control

There is a wealth of evidence that poor glycaemic control of diabetes increases the risk of the development and progression of DR in both type 1 and type 2 diabetes.(Engerman et al. 1977, Pirart 1978, Ballard et al. 1986, Nathan et al. 1986, Klein et al. 1988, 1989b, a, Brinchmann-Hansen et al. 1992, Davis et al. 1998) Two landmark clinical trials the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) showed that achieving near normo-glycaemia delays both the onset and retards the progression of DR.(The Diabetes Control and Complications Trial Research Group 1993, UK Prospective Diabetes Study group 1998b, c)

In the primary prevention group (those without DR at baseline) of the DCCT, in type 1 diabetes conducted over a mean 6.5 years follow up period the frequency of progression of DR was reduced by 76% in the intensive treatment group compared to the usual care group.(The Diabetes Control and Complications Trial Research Group 1993) In the secondary prevention group the corresponding risk reduction was 54% (Figure 1.3.3). The long term follow up 10 years of this study group has demonstrated a residual protective effect on DR of this early tight control despite subsequent comparable glycaemic control (metabolic memory).(White et al. 2010, Aiello et al. 2014) However, there are some persons with poor glycaemic and blood pressure control who never develop DR even over prolonged periods of time, whilst other will develop DR despite good control of risk factors. In the Medalist study 50%

of older persons did not develop DR despite having type 1 diabetes for over 50 years.(Keenan et al. 2007)

Figure 1.3.3: Cumulative incidence of DR in persons with type 1 diabetes receiving intensive or convention therapy in the DCCT trial A) Primary prevention cohort, B) secondary prevention cohort (The Diabetes Control and Complications Trial Research Group 1993)



The UKPDS included persons with type 2 DM showed that a reduction of mean HbA_{1c} from 7.9% to 7.0% over 9 years was associated with a 21.0% reduction in the risk of progression of retinopathy over 10 years.(UK Prospective diabetes study group 1998c) Similar reductions in risk were observed for obese subjects treated with metformin rather than sulphonylureas or insulin, indicating that it was the reduction in glycaemia rather than the type of treatment that was of significance.(UK Prospective Diabetes Study group 1998b) Long term follow up of the UKPDS has also shown that despite early loss of glycaemic difference, there was a continued reduction in microvascular risk during 10 years of post trial follow up referred to as the legacy effect.(Holman et al. 2008a)

The Steno-2 trial was a target driven, intensified, multifactorial intervention of modifiable risk factors compared to conventional treatments in persons with type 2 diabetes and microalbuminuria.(Gaede et al. 2003) The intensive therapy

intervention included; a dietary intake of fat <30% and saturated fatty acid <10% of the daily energy intake, light-moderate exercise 30 minutes 3-5 times per week, prescription of an ACE inhibitor or an angiotensin II-receptor antagonist irrespective of blood pressure level, a vitamin-mineral supplement, aspirin, oral hyperglycaemic agents (OHA) was added HbA_{1c} <6.5% could not be maintained after 3 months, if HbA_{1c} >7.0% despite maximal doses of OHAs then insulin therapy was initiated, raised fasting serum cholesterol levels were treated with statins and hypertriglyceridaemia was treated with fibrates. The study found a 57% reduction in risk of DR for persons in the intensive treatment group over an 8 year period. The action to control cardiovascular risk factors in diabetes (ACCORD) trial assessed the effects of intensive glycaemic control, lipid control and intensive hypertensive therapy on cardiovascular events and the progression of DR.(ACCORD study group et al. 2010) Intensive glycaemic control was found to significantly reduced the risk of progression of DR after 4 years.

There have however, been two trials, the action in diabetes and vascular disease: Preterax and Diamicon MR controlled evaluation trial (ADVANCE) and Veterans affairs diabetes trial (VDAT) trials, involving persons with type 2 diabetes that have reported no significant reduction in the incidence or progression of DR following intensive glycaemic control. The ADVANCE trial looked at the effects of blood pressure lowering and intensive glycaemic control (targeting a HbA_{1c} ≤6.5% in persons with type 2 diabetes over a period of 4.1 years.(Beulens et al. 2009) There was a borderline significant reduction in the risk of microaneurysms, exudates and macular oedema associated with intensive glycaemic control. The authors concluded that a longer follow up period and a greater number of patients were required for intensive glycaemic control to result in significant risk reductions in DR. The VDAT trial examined the effects of lowering HbA_{1c} levels by 1.5% in veterans with type 2 diabetes over a median follow up period of 5.6 years.(Duckworth et al.

2009) The study reported a non-significant trend towards an increased incidence in severity of DR in the standard therapy group.

1.3.2.3 Blood pressure

Although there is some inconsistency in the evidence it is generally accepted that hypertension is an independent and important risk factor for the development of microvascular complications in diabetes.(Knowler et al. 1980, Klein et al. 1984b, Ballard et al. 1986, Klein et al. 1995) The UKPDS and appropriate blood pressure control in diabetes (ABCD) trials demonstrated the importance of hypertension as a risk factor for micro- and macro-vascular complications in type 2 diabetes.(Schrier et al. 1996, Kohnner et al. 1998, UK Prospective diabetes study group 1998a, Estacio et al. 2000, Schrier et al. 2002) However the more recent ACCORD and ADVANCE trials did not find a beneficial effect of lowering blood pressure on DR.(Beulens et al. 2009, ACCORD study group et al. 2010)

In the UKPDS study severity of DR was related to both systolic and diastolic blood pressure at entry into the study.(Kohnner et al. 1998) Over nine years, a reduction in mean blood pressure from 154/87 mm Hg to 144/82 mmHg resulted in a 34% lower risk of progression of DR and a 47% lower risk of significant reduction in visual acuity.(UK Prospective diabetes study group 1998a) For each 10mmHg decrease in mean systolic blood pressure there was a 13% reduction in the incidence of DR with no apparent threshold. However, these benefits were not sustained post trial once the differences in blood pressure between the groups were lost 2 years after the end of the trial.(Holman et al. 2008b) The results of the ABCD showed over a 5 year follow up period there was no difference between the intensive and moderate control groups with regards to progression of DR.(Schrier et al. 1996, Estacio et al. 2000, Schrier et al. 2002) This trial may suggest the possibility of a threshold effect

below which only minimal efficacy for reducing the risk of progression of DR is achieved by further reductions in blood pressure.

The more recent ADVANCE and ACCORD trials however, could not confirm the influence of blood pressure lowering on progression of DR.(ADVANCE Collaborative Group 2007, ACCORD study group et al. 2010) The UKPDS trial had higher baseline and achieved a greater reduction in blood pressure values than either ADVANCE or ACCORD. Therefore leaving investigators to postulate that blood pressure control was more effective in poorly controlled hypertension or that a longer follow up time was required to observe the effects on DR progression at lower levels of blood pressure.

Recent studies have focused on the renin-angiotension system (RAS). The EUCLID controlled trial of Lisinopril (an angiotensin convertase enzyme [ACE] inhibitor) showed a significant reduction in the progression of DR.(Chaturvedi et al. 1998) The diabetic retinopathy Candesartan trials (DIRECT) (tested the efficacy of Candesartan an angiotensin receptor blocker on DR) found that Candesartan reduced the incidence of DR by 18% but did not significantly affect its progression,(Chaturvedi et al. 2008, Sjolie et al. 2008) in persons with type 1 diabetes. However, regression of early DR was shown in persons with type 2 diabetes.(Sjolie et al. 2008) These studies have also found that the use of ACE inhibitors or angiotension II receptor blockers have effects beyond that of blood pressure control as progression of DR was reduced even in those normotensive persons.(Lingam et al. 2013) This may be due to ACE inhibitors having a direct effect on the eye as some studies have shown that ACE is produced locally by vascular endothelial cells which may affect retinal flow and vascular structure.(Chaturvedi et al. 1998)

1.3.2.4 Lipids

If the effects of blood pressure control on the incidence and progression of DR have been inconsistent in clinical trials, then the impact of lipid control have been even more inconsistent. The EURODIAB study, identified triglyceride levels as a significant risk factor for moderate and severe non PDR (NPDR) and PDR (standardised relative risks (RR) 1.4, 1.3 and 1.6 respectively).(Sjolie et al. 1997) Evidence from the earlier ETDRS indicated that elevated triglycerides were an independent risk factor for the development of high risk PDR. (Davis et al. 1998) Elevated total cholesterol and low density lipoprotein cholesterol (LDL-cholesterol) levels were also seen to be associated with twice the risk of having hard exudates at entry into the study and about one and a half times the risk of developing hard exudates during the study, whereas other lipoprotein fractions and triglycerides were not.(Davis et al. 1998) In the WESDR study in persons using insulin (irrespective of age at onset) higher total serum cholesterol was associated with increased odds of having retinal hard exudates.(Klein et al. 1999) However, there was no relationship between total cholesterol and high density lipoprotein-cholesterol (HDL-cholesterol) with DR or with hard exudates in the older onset age group not using insulin.(Klein et al. 1991) The STENO-2 study found a 67% significant reduction in DR in the intensive intervention group involving multiple risk factors, including glycaemic control, blood pressure, cholesterol and microalbuminuria over 4 years, which was sustained at 8 years.(Gaede et al. 1999, Gaede et al. 2003) However these findings have not been universally consistent.(Duncan et al. 1968, Sjolie et al. 1997, Colhoun et al. 2004, Thomason et al. 2004)

The use of fibrates have been shown to have a beneficial effect on retinal exudates (Harrold et al. 1969, Dorne 1977, Rencova et al. 1992, Freyberger et al. 1994,

Keech et al. 2007, ACCORD study group et al. 2010, Morgan et al. 2013) and macular oedema.(Cullen et al. 1964, Duncan et al. 1968) The Fenofibrate Intervention and Event Lowering in Diabetes study (FIELD) reported that persons with type 2 diabetes treated with fenofibrate, in addition to therapies for hyperglycaemia and other risk factors for DR, were less likely to need laser therapy than controls.(Keech et al. 2005) There was also less progression of pre-existing DR with fenofibrate. However, in persons without pre-existing DR there was no significant reduction in the progression to DR.(Keech et al. 2007) This was also confirmed in the ACCORD eye study which aimed to determine whether any one of three interventions in the main ACCORD trial being intensive glycaemic therapy, the addition of fenofibrate to a statin and intensive blood pressure therapy reduced the risk of development or progression of DR compared to standard treatments.(ACCORD study group et al. 2010) However a retrospective matched cohort study found that treatment with fibrates was associated with a 20% reduction in the rate of first onset DR.(Morgan et al. 2013) This reduction in the onset of DR did not appear to be attributable to the lipid lowering effects of fibrates. Other non-lipid-related mechanisms that may explain the effect of fibrates on DR are the anti-inflammatory and antioxidant properties of fibrates.(Poynter et al. 1998, Delerive et al. 1999) Fenofibrate acid has also been reported to prevent the disruption of the retinal pigment epithelium cells and prevent the increased breakdown of the blood-brain capillary barrier and downregulation of vascular endothelial growth factor (VEGF).(Meissner M et al. 2004, Trudeau K et al. 2011, Villarroel M et al. 2011) In addition fibrates possess neuroprotective properties.(Bordet R et al. 2006)

1.3.2.5 Other risk factors

Ethnicity

Ethnic origin differences in the prevalence of DR have been a focal point of interest in recent research.(Cheung et al. 2010) Prevalence of DR and ethnic origin associations with the presence of any DR and also severe/referable stages of DR have previously been reported to be higher in non-Caucasian persons when compared with Caucasians.(West et al. 1982, Ross et al. 2007, Stolk et al. 2008, Raymond et al. 2009) However, while variability in frequency may reflect true differences in prevalence; lack of uniformity in study designs, protocols for examination and documentation may explain some of the differences.(Klein et al. 2003) There may also be differences in environmental and genetic risk factors as well as other covariates that may have a marked impact on frequency.

Pregnancy

Pregnancy may accelerate the incidence and progression of DR. Pregnancy was found to be independently associated with the progression of DR in both the WESDR and the DCCT.(Klein et al. 1990, The Diabetes Control and Complications Trial Research Group 2000). Several factors related to metabolic changes (hyperglycaemia), type of diabetes (duration of diabetes prior to conception, baseline DR status), pregnancy itself (hypervolaemia and hypercoagulation, impaired retinal autoregulation) and complications of pregnancy (pre-eclampsia) all seem to play an important role in the progression of DR during pregnancy.(Kaaja et al. 2007) However, unless DR has progressed to pre-proliferative DR (PPDR) or PDR stages pregnancy seems to have no long term detrimental effects with regards to progression. It has been suggested that fundal examinations be conducted in pregnant women with diabetes in the first trimester and then once every 3 months following the initial examination and importantly 3 months post-natal.

Genetics

It seems likely that both genetic and environmental confounders exist for the development of DR, especially in light of the evidence that some persons with short duration of diabetes and good glycaemic control still develop DR and some with long duration and hyperglycaemia do not. (Nathan 1993, The Diabetes Control and Complications Trial Research Group 1993) There was also some evidence indicating significant correlations between the severity of DR in family members from the DCCT study and others, (The Diabetes Control and Complications Trial Research Group 1997, Alcolado 1998) and increased risks in siblings of affected persons. (Leslie et al. 1982) Heritability has been estimated to be as high as 27% for DR and 52% for PDR. (Looker et al. 2007, Hietala et al. 2008) However, currently our understanding of the relationship between genetics of DR is limited. It is thought that current studies assessing genome wide associations offer greater promise in our understanding the genetic architecture of DR susceptibility. (Liew et al. 2009, Cho et al. 2014)

1.4 Treatment of diabetic retinopathy

As discussed in section 1.3 above, tight glycaemic and blood pressure control are the cornerstones in the primary prevention of DR with some evidence of benefits with the use of fibrates. (Mohamed et al. 2007) Currently treatment once DR is established is by photocoagulation for selected cases of severe NPDR and PDR and vitrectomy if DR continues to worsen despite adequate photocoagulation treatment. There is also the recent addition of anti-VEGF treatment for CSMO with some benefits seen for PDR.

Diabetes emerged as a leading cause of vision loss by 1968, therefore clinicians attempted to develop the tools and means to preserve vision. Some of these were

invasive such as partial pituitary ablation but there were complications related to hypopituitarism, which included death.(Antonetti et al. 2012) Other attempts were as simple as one aspirin per day. Therefore prognosis for vision during this time was poor. Pan retinal photocoagulation was first used to treat retinal disease in the 1950s, and is now an established technique for treating severe NPDR and PDR.(Kapany et al. 1963, Meyer-Schwickerath 1967) Randomised controlled trials in the 1960s, 1970s and 1980s confirmed the benefit of laser photocoagulation in the treatment of DR and maculopathy to prevent vision loss.(Diabetic Retinopathy Study Research Group 1976, 1981a, b, British Multicentre Study Group 1984, Early Treatment Diabetic Retinopathy Study Research Group 1991a) The best response was observed in early PDR, whereas advanced neovascularisation and gliosis showed little improvement. However photocoagulation is a destructive process burning the retina and thereby destroying the cells and vision and so should not be used too early in the course of the development of DR.

Removal of all or part of the vitreous by pars plana vitrectomy was first advocated in the early 1970s.(Machemer et al. 1972) Evidence from trials have demonstrated that vitrectomy performed in eyes with good visual acuity and early evidence of traction detachment had good preservation of vision in 73% of cases.(Shea 1983, Diabetic Retinopathy Vitrectomy Study Research Group 1985) In the Diabetic Retinopathy Vitrectomy Study (DRVS) significant benefit was seen only in persons with type 1 diabetes and not in type 2 diabetes.(Diabetic Retinopathy Vitrectomy Study Research Group 1985)

Further clinical trials in the 1980s evaluated the benefit of laser treatment in maculopathy.(British Multicentre Study Group 1983, Early Treatment Diabetic Retinopathy Research Study Group 1985) They found that significant visual loss in treated eyes was approximately half that in untreated eyes. Eyes showing evidence

of CSMO were particularly likely to benefit, and the presence of CSMO was an indication for focal treatment even if visual acuity was normal.

In 1999, intravitreal injections of corticosteroids (triamcinolone acetonide) were proposed as a treatment for diabetic macular oedema. A treatment thought to be effective for its anti-inflammatory properties and as it was demonstrated to inhibit the expression of the VEGF gene.(Nauck et al. 1998) Initial findings from studies of intravitreal triamcinolone acetonide (IVTA) were positive showing improvements in retinal thickness and visual acuity.(Martidis et al. 2002, Jonas et al. 2003) However these improvements appear to be short term.(Bressler et al. 2009, Rudnisky et al. 2009, Yilmaz et al. 2009, Elman et al. 2011, Jampol et al. 2014) The adverse effect of IVTA most commonly reported was raised intraocular pressure, additionally cataract formation or progression, endophthalmitis and retinal detachment have been reported.(Yilmaz et al. 2009)

In 2006 attention turned to the use of intravitreal injections of anti-VEGF medications.(Jampol et al. 2014) Anti-VEGF agents have to be injected directly into the vitreous body at regular intervals. There are currently four anti-VEGF drugs available for the treatment of diabetic macular oedema that have been extensively investigated: pegaptanib, bevacizumab, ranibizumab and aflibercept. Clinical trials have indicated that vision can be improved with repeated injections.(Cunningham et al. 2005, Massin et al. 2010, Michaelides et al. 2010) Use of bevacizumab and ranibizumab have been shown to improve visual acuity by an average of one to two lines on a Snellen chart, with an improvement of 3 lines or more in 25% to 30% of people, and the loss of visual acuity decreased by one third.(Arevalo et al. 2007, Massin et al. 2010, Michaelides et al. 2010) Pegaptanib improved visual acuity by approximately one line.(Cunningham et al. 2005) Some studies have also shown beneficial effects of the use of intravitreal bevacizumab in conjunction with

photocoagulation on PDR as well as prior to vitrectomy.(Tonello et al. 2008, Ahmadieh et al. 2009, Cho et al. 2009) The use of intravitreal bevacizumab resulted in a greater reduction in active leaking new vessels, and preventing visual dysfunction and foveal thickening and rapid resolution of vitreous haemorrhage. The use of intravitreal bevacizumab prior to pars plana vitrectomy prevented re-bleeding and accelerated postoperative vitreous clear up. However, intravitreal injection of anti-VEGF therapies have systemic and ocular adverse risks the most damaging of which is infectious endophthalmitis. Other ocular risks are inflammation, rhegmatogenous retinal detachment, raised intraocular pressure, and subretinal haemorrhage.(Ghasemi Falavarjani et al. 2013) Despite the adverse risks, the need for monthly injections and related costs, anti-VEGF therapies are slowly becoming the preferred therapy for CSMO. NICE guidelines recommends their use if the central retinal thickness is ≥ 400 microns and they are also currently under investigation for use in PDR with or without laser.(NICE 2013)

Other treatments for DR currently being investigated involve the blockage of RAS system, (Chaturvedi et al. 2008, Sjolie et al. 2008) and the use of protein kinase-C (PKC) inhibitors, (PKC-DRS study group 2005, Aiello et al. 2006, Aiello et al. 2007) which have shown some positive results. However, further investigation into these new therapies is required before they are recommended for use in the treatment of DR.

1.5 Detection of diabetic retinopathy

1.5.1 History of the ophthalmoscope and retinal photography

The retina was first visualised in 1704 by Jean Mery who saw the retinal vessels in the fundus after placing a cat under water.(Keeler 2003) Jan Purkinje then used his myopic glasses to reflect candle light placed behind a dog to visualise the fundus in

1825. In 1846 William Cumming published his findings that every eye could be visualised if the light source directed towards the subjects eye and the observers line of sight were coincident.(Cumming 1846) In 1851 Hermann Von Helmholtz invented the first ophthalmoscope (Figure 1.5.1).(Keeler 2003) The ophthalmoscope underwent many design changes during the 19th and 20th century and by 1913 Edward Landolt reported that over 200 models had been produced.

Figure 1.5.1: a) Early Helmholtz ophthalmoscope (www.college-optometrists.org) (1851), b) modern day Keeler direct ophthalmoscope (www.keeler.co.uk)
a) b)



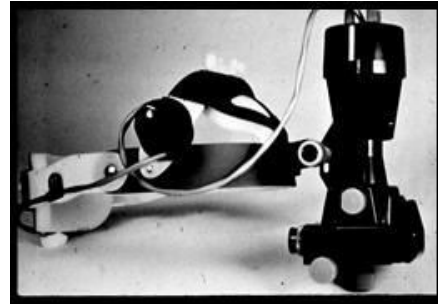
Two years after the first ophthalmoscope was developed Reute invented the indirect ophthalmoscope, which allowed a wider stereoscopic view of the fundus.(Avanced retinal imaging laboratory 2014) This allowed the periphery of the retina to be viewed even through slightly hazy media (Figure 1.5.2). The golden age of ophthalmology became evident following these first two inventions with the discovery of pigment retinopathy and detachment of the retina in 1853, DR, retinal vein occlusions and glaucoma in 1855, hypertensive retinopathy in 1856, syphilitic retinitis in 1858 and embolism of the central retinal vein in 1859.

Figure 1.5.2: a) first indirect ophthalmoscope, b) modern day indirect ophthalmoscope. (www.nyee.edu)

a)

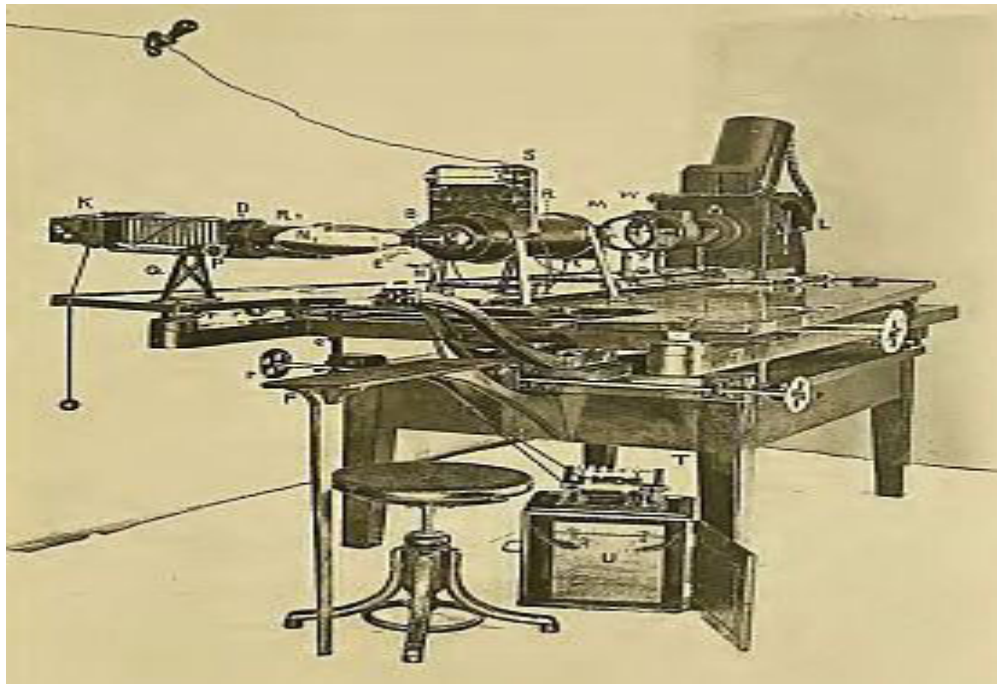


b)



The first photographs of the retina were obtained from a rabbit, and were produced in 1862 by Dr Noyes. (Van Cader 1978). The photographs were captured using Frederic Scott Archer's wet plate method of coating glass plates with a photographic surface. It was another 20 years before anyone attempted to photograph a human subject. This was achieved by Jackson and Weber in 1886, using a small camera attached to the head of a patient and an ophthalmoscopic mirror placed at 45° to the camera lens, which deflected light from a source placed near the ear of the patient. However, due to constriction of the pupil after the flash of light, the lack of colour and a large central artefact associated with retinal photography, ophthalmic artists were employed to produce accurate drawings of the retina. In 1871, the wet plate was replaced with a plate that could be used dry, the photographic emulsion developed by Dr Maddox. In 1907, Dimmer published the first ever atlas of fundus photography using a fundus camera that was so large and expensive only one was ever built by Zeiss (Figure 1.5.3) (Same 1993).

Figure 1.5.3: Dimmer-Zeiss fundus camera (www.opsweb.org)



The first widely used camera, the Zeiss-Nordenson, was created in 1925 designed by Dr Nordenson with the Zeiss company (Figure 1.5.4). The camera had a 10° field of view and required a 0.5 second exposure with colour film. In the mid 1920s 35mm rolled film was produced for the camera. This nitrate film ended the need for fragile glass plates. In 1929, Bedell published his atlas of stereo fundus photographs, the same year colour fundus photography was attempted. (Same 1993) Between 1931 and 1950 retinal photography gained favour, however slow film and long shutter speeds meant obtaining quality images was difficult. In 1955 the Zeiss-Littmann camera was produced which was a fully adapted fundus camera with electronic flash, better optics and an affordable price, imaging the central 30° pole of the retina.

Figure 1.5.4: Zeiss-Nordenson fundus camera (www.museumofvision.org)



In the 1970s, Nikon developed the first wide angle fundus camera at 45°. Fundus cameras in use today feature variable wide angle lenses ranging from 15° to the full fundus view (from pole to pole). In the 1990s Polaroid film began being used to record retinal images. In the 1980s non-mydratic 45° cameras were introduced in the UK originally using 35mm film followed by Polaroid film and now digital imaging.

1.5.2 Methods of screening for diabetic retinopathy

There are several methods currently available for visualising the retina, including direct ophthalmoscopy, fundus photography, slit lamp biomicroscopy and fluorescein angiography. Fluorescein angiography is held as the gold standard for detecting DR, however there are side effects to fluorescein making it less desirable

for general population screening. Deciding on the best method for screening has been the subject of much debate. Direct ophthalmoscopy with mydriasis was shown to have a sensitivity of 65% when used by ophthalmologists, 33-66% general practitioners and 48-83% optometrists, (Harding et al. 1995, Owens et al. 1998, Younis et al. 2002) falling short of the >80% sensitivity for detecting DR recommended by the Exeter standards.(British Diabetic Association 1997) Indirect ophthalmoscopy using slit lamp biomicroscopy and Volk lenses by ophthalmologists and optometrists had a sensitivity of 91% and specificity of 95% for the detection of sight-threatening DR.(Moss et al. 1985, Kleinstei et al. 1987) The widespread availability was an advantage for this method of detection however, slit lamp biomicroscopy requires considerable skill and the procedure could be time-consuming. The National Screening Committee (NSC) also had concerns with this method for use in screening programmes as quality assurance would be difficult to assess.(Garvican et al. 2000)

In comparison with direct ophthalmoscopy, retinal photography by non-mydriatic cameras with mydriasis has been shown to have adequate sensitivity at >80%, therefore meeting the Exeter standards for screening. Non-mydriatic and mydriatic photography was compared by Moss in 1985 with equivalent agreement between the methods (82.5% and 86.5% respectively).(Moss et al. 1985) However, non-mydriatic photography without mydriasis has been shown to be less sensitive mainly due to the pupillary constriction of the second eye following flash photography in the first.(Younis et al. 2002) Therefore, retinal photography with non-mydriatic cameras following dilation was the recommended method for screening in the UK.(Garvican et al. 2000, The National Screening committee 2000)

Earlier debates regarding the method of screening has been the use of Polaroid vs. 35mm film. Advantages of Polaroid film were the availability of an immediate image

allowing discussion with the patient at the time of appointment. However Polaroid film was found to have poor resolution, could fade, was expensive, difficult to store and easy to lose from patient files.(Taylor 1996) 35mm film was found to have a much higher resolution but the films took several days to develop. Both of these media have now been overtaken with the advancement of digital photography which was found to be comparable with 35mm in sensitivity and specificity for detecting sight-threatening DR.(Li et al. 2010b) Even compression of the images did not compromise gradeability.(Li et al. 2010a)

Digital photography has several advantages over its predecessors. In comparison to direct and indirect ophthalmoscopy there is the creation of a permanent record, reduced time requirements and a lower skill level to achieve similar levels of sensitivity and specificity. In comparison to Polaroid and 35 mm film there are fewer storage issues and less chance of the images fading or being destroyed. Also the advances in computer technology allow for easier manipulation of images and therefore easier grading, storage and analysis. Camera based screening with digital storage of images is the preferred option for screening.(Garvican et al. 2000)

Following the introduction of digital imaging and the continuing debate over the number of fields required to adequately classify DR, recent advancements have included the development of widefield scanning laser ophthalmoscopy and optical coherence tomography,(Virgili et al. 2007, Wilson P J et al. 2010, Wessel et al. 2012, Prescott et al. 2014) which maybe incorporated into screening in the future.

1.5.3 Screening for diabetic retinopathy

Screening is defined as “*the process of examining a group of people for the presence of a disease*” (Wilson et al. 1968) with its prerequisites being:

- The disease must appear in a defined population
- The population must be identifiable
- The disease must present a health problem
- There must be effective treatment for the disease
- Screening must be cost effective and improve quality of life (Kohner 1993)

As photocoagulation is an effective treatment for PDR especially when applied in the early stages of PDR when it remains asymptomatic, widespread screening for DR has been advocated. In 1989, the St. Vincent Declaration (International Diabetes Federation 1990) identified strategies for the control of chronic diseases in developed countries. The key five year targets for diabetes were '*to elaborate, initiate and evaluate comprehensive programmes for detection and control of diabetes and its complications*' and to '*implement effective measures to reduce new blindness due to diabetes by one third or more*', among other directives relating to cardiovascular disease, renal disease and amputations.

A protocol for screening for DR and a field guide for those involved in screening in Europe was published in 1991. (Retinopathy Working Party 1991) It stated that the cost of organising nation-wide screening was substantially lower than the costs involved in late and often unsuccessful treatment and supportive care for people who had become blind.

Screening in the UK remained patchy throughout the 1990s and in those areas where screening was taking place different methods were in use (direct

ophthalmoscopy by physicians/GPs, community or hospital based retinal photography and ophthalmoscopic examination by optometrists).(Younis et al. 2002) The methods used were dictated by several factors including local policy, historical activity and funding issues.

Thompson et al surveyed health authorities between 1994-95, whilst Bagga et al surveyed diabetologists in 1996 to find out if they had a policy on screening for DR and if they were purchasing screening services.(Bagga et al. 1998, Thompson et al. 1999) They concluded that DR screening was in a period of transition and that whilst the St Vincent declaration had served as an important catalyst for change in the UK the direction in which service provision was developing was less clear. In 1999 the Royal College of Ophthalmologists together with Diabetes UK, developed plans for a national screening programme in England, Wales, Scotland and Northern Ireland to combat the adhoc nature in which they had been set up historically.(Garvican et al. 2000) The National Service Framework (NSF) for diabetes was published in 2001 for England and in 2002 for Wales.(Department of Health 2001a, Welsh Assembly Government 2002) Both documents set out key directives necessary to raise the standards of care for diabetes. One of the key recommendations for DR was the need for regular surveillance of adults with diabetes and early laser treatment of those identified with sight-threatening DR, which would then reduce the incidence of visual impairment and blindness in persons with diabetes. In conjunction with the NSF, the NSC and the National Institute for Clinical Excellence (NICE) published guidelines and recommendations for the preservation of sight in persons with diabetes. (Department of Health 2001b, National Institute for Clinical Excellence 2002) The primary objective was to identify all undiagnosed sight-threatening DR and facilitate timely onwards referral to hospital eye services (HES). The secondary objective was to identify the presence

of any DR so that improvements in glycaemic control, hypertension and dyslipidaemia could be implemented where necessary.

1.5.4 Screening intervals for diabetic retinopathy

Annual screening was recommended by the clinical standards advisory group on standards of care for people with diabetes,(Grewing et al. 1994) by the then British Diabetic Association (BDA, now Diabetes UK) specialist workgroup on visual handicap,(Kohner et al. 1996) and in guidelines for DR issued by the Royal College of Ophthalmologists.(Royal college of Ophthalmologists 2005) This recommendation was made based on expert opinions, as there was no evidence from clinical trials or observational studies on which to base this recommendation. The annual timescale also fitted with the annual review for people with diabetes conducted in general practice. However, it was at the time proposed that this situation would be re-evaluated when established screening programmes had additional data available. Although screening for DR has been shown to be cost effective, DR screening programmes are expensive.(Javitt et al. 1989, James et al. 2000) In these times of increasing healthcare expenditure, all services are under increased pressure to be as cost effective as possible, with prudent healthcare being very much promoted in Wales.(1000 lives improvement service in Public Health Wales 2014) Extending the screening interval in those at low risk could improve the cost effectiveness of DR screening programmes (Rein et al. 2011, Chalk et al. 2012) and meet the principle of prudent healthcare of *'delivering the best-evidence based treatment and services to the most appropriate level, based on individual need.'*(1000 lives improvement service in Public Health Wales 2014)

There is evidence from small screening programmes in the UK, Iceland, Italy, Sweden and Denmark that extending the screening interval in persons without DR

is safe (Younis et al. 2003a, Younis et al. 2003b, Olafsdottir et al. 2007, Agardh et al. 2011, Aspelund et al. 2011, Jones et al. 2012, Looker et al. 2013, Porta et al. 2013, Stratton et al. 2013) and cost-effective.(Chalk et al. 2012)

In the UK, Younis et al demonstrated that screening intervals could safely be extended to once every five years in persons with type 2 diabetes and type 1 diabetes without evidence of DR.(Younis et al. 2003a, Younis et al. 2003b) However, a maximum screening interval of once every 2-3 years was recommended due to a possible fall in compliance if screening intervals were overly long. Jones et al also demonstrated that the incidence of referable DR (RDR) and PDR in persons with type 2 diabetes without evidence of DR was sufficiently low to allow extension of the screening interval beyond annual, although they stopped short of recommending a screening interval.(Jones et al. 2012) Stratton et al suggested that the risk of developing sight-threatening DR is different even among persons without DR at first screening.(Stratton et al. 2013) They, therefore suggested that the DR results from two sequential annual screening visits should be combined to determine the level of risk and inform the screening intervals. Looker et al also suggested that a screening interval of once every two years could be appropriate for persons without evidence of DR at two consecutive screening events, resulting in a 40% reduction in people screened.(Looker et al. 2013) In addition the four nations in the UK are expected to report to the NSC on findings from a research project combining datasets from 4 screening programmes in England, as well as the National screening programmes in Wales, Scotland and Northern Ireland.(Four Nations Study Group 2013)

In Denmark, Aspelund et al used a mathematical algorithm to set screening intervals for each person based on clinical risk factors such as diabetes type, duration of diabetes, glucose control, blood pressure and the level of DR.(Aspelund

et al. 2011) The conclusions of this study were that the same results were achieved through individualised screening as annual screening with 59% fewer examinations. In Iceland screening intervals for persons without DR have been extended to biennial, and over a 10 year period no person experienced a delay in treatment of DR.(Olafsdottir et al. 2007) On detection of DR annual screening is reinstituted. Whilst in Sweden, screening intervals have been extended to triennial for persons with type 2 diabetes, under good glycaemic control ($6.4\% \pm 1.4$), with a short duration of diabetes (6 years) and without DR.(Agardh et al. 2011) At the three year follow up screening no person had developed PDR and only three people had developed macular oedema, however only one person required treatment. Porta et al in Italy has recommended biennial screening in all persons without DR.(Porta et al. 2013) They also suggested the possibility of further stratifying the screening interval as persons using insulin with a long duration diabetes (≥ 10 years) progressed more rapidly to RDR than those not using insulin with a shorter duration of diabetes. Evidence from large scale screening programmes and populations with access to more putative risk factors than screening programmes routinely collect prior to this study however, is lacking.(Thomas et al. 2012)

1.6 Aims and Objectives of this Thesis

The aim of my study was to determine the epidemiology of DR in Wales, UK based on the National Diabetic Retinopathy Screening Service for Wales (DRSSW). Therefore the prevalence and incidence of DR was estimated and the limited putative risk factors collected by the DRSSW were assessed for their association with the development and or progression of DR. The screening interval for DR in Wales is currently annual for all persons with diabetes. Therefore this thesis aimed to determine whether annual screening was necessary in persons with diabetes without DR at screening, or if a longer screening interval could be safely introduced.

In addition the prevalence and incidence of DR was also assessed in a population undergoing screening within a private diabetes management programme in Johannesburg, South Africa. This second data set provided a unique opportunity to assess additional putative risk factors and their association with the development of DR over a longer period of time, but in a small sized population. It also provided an opportunity to assess whether annual screening for DR in persons with diabetes but without evidence of DR was necessary in other ethnically diverse populations.

This study addresses these issues by retrospective analysis of the DRSSW and the centre for diabetes and endocrinology (CDE) in Johannesburg, South Africa databases. The DRSSW is a national screening programme providing a large database, whilst the CDE is a smaller diabetes management programme providing data on a much wider range of putative risk factors. As assessment of visual acuity forms part of the screening procedures an additional aim of this thesis was to assess the level of visual impairment and blindness within both the DRSSW and CDE.

Chapter 2

Materials and Methods

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2.1 Diabetic retinopathy screening

2.1.1 Screening methods

Several methods including direct and indirect ophthalmoscopy and retinal photography have been used to visualise the retina to permit the detection and assessment of DR. Direct ophthalmoscopy has been shown not to have adequate sensitivity (49%) for screening for DR.(Sussman et al. 1982) Indirect ophthalmoscopy with slip lamp biomicroscopy has been shown to have adequate sensitivities (96%) and specificities (93%) for screening however, the method required considerable skill and training.(Sussman et al. 1982, Garvican et al. 2000) Retinal photography with images captured on 35mm film by a specially trained technician was proven to have higher sensitivities and equivalent specificities compared to direct ophthalmoscopy performed by an experienced ophthalmologist (sensitivity 89% vs. 65% and specificity 86% vs. 97%).(Harding et al. 1995) Retinal photography (35mm film) also has the added benefits of a permanent record, beneficial for quality assurance.

Initially retinal photography for screening purposes was captured using Polaroid images. The benefit of this was that the image was available immediately, however the images were often lost from patient's records and would degrade over time. In contrast 35mm film provided better quality images,(Jones et al. 1988) with a higher resolution over Polaroid, with the benefits of not degrading. However, the time taken to develop 35 mm film at approximately 5 days to allow grading was a distinct disadvantage and also did not allow images to be shared with patients at the time of appointment. Studies assessing the performance of 35mm film vs. Polaroid have demonstrated that using 35mm film had a better detection of DR lesions.(Pardhan

et al. 1991) In more recent years the advent of digital cameras has allowed improved storage of images with the added benefit of the image being immediately available and also providing the possibility of image enhancement and analysis. Studies have shown close agreement (weighted kappa 0.88) between digital images and 35mm film,(George et al. 1998, Henricsson et al. 2000) and improved detection of DR and sight-threatening DR compared to Polaroid images.(Ryder et al. 1998)

2.1.2 Screening for DR in Wales, UK

During the early 1990s, there were many different methods of screening in operation in England and Wales including ophthalmoscopy and retinal photography (Polaroid and 35 mm film).(Younis et al. 2002) The Welsh community diabetic retinopathy study (WCDRS), funded by the department of health, set out to compare the different methods of screening i.e. direct ophthalmoscopy versus retinal photography (two 45° field Polaroid film or 35mm colour film transparencies) following mydriasis at general practice (GP) locations.(Gibbins et al. 1998, Owens et al. 1998, Gibbins 1999) The study recruited 644 persons with diabetes from four GPs in Wales who subsequently attended two screening sessions, over a three year period. A validated grading system for DR was used, which was derived by the European (St. Vincent) DR working group.(Kohner et al. 1990) Clinical ophthalmoscopy was performed by both GPs and optometrists whilst the retinal images were assessed by a diabetologist in addition to the GPs and optometrists.

In this community setting, retinal photography was shown to be a more sensitive screening technique for detecting sight-threatening DR than direct ophthalmoscopy with sensitivities ranging from 87.3% to 97.1% for 35mm or Polaroid film vs. 67.1% to 82.2% for ophthalmoscopy and specificities of 82.7% to 87.4% vs. 88.5% to

93.8% respectively.(Gibbins et al. 1998) It was apparent that, whoever acted as assessor (GP or community optometrist or specialist optometrist), the use of 35mm retinal photographs improved sensitivity for the detection of sight-threatening DR by between 10% and 20% compared to ophthalmoscopy (GP 79.2% vs. 62.6%, community optometrist 73.9% vs. 88.2% and specialist optometrist 69.9% vs. 86.1% respectively). This observation had also been demonstrated in other previous studies.(Buxton et al. 1991, Peters et al. 1993, Harding et al. 1995)

In addition, the WCDRS also demonstrated that it was possible to organise an effective mobile screening service for DR in a community setting, involving three regional health authorities in South Wales. Through the close co-operation between different health care sectors, with the then 'high' prevalence rate of known diabetes at 2.1%, there was a high attendance rate (84.3%) at screening sessions.(Gibbins et al. 1989, Owens et al. 1998, Gibbins 1999)

Following the WCDRS a pilot regional mobile DR screening programme was commissioned in 1998 by the Bro-Taf Regional Health Authority in South Wales. This initial Bro-Taf DRSS proved that community based mobile screening could be provided on an annual basis for a population of approximately 19,000 persons with diabetes within the regions of Cardiff, Rhondda Cynon Taf, Merthyr Cynon and Vale of Glamorgan. Subsequently in 2002, following the success of the Bro-Taf regional screening programme, the National DRSSW was commissioned by the Welsh government to meet one of the objectives of the National Service Frameworks for Diabetes in Wales.(Welsh Assembly Government 2002)

2.1.2.1 Diabetic retinopathy screening service for Wales, UK

In 2003, the DRSSW moved into its permanent base at Treforest, just outside Cardiff, (Figure 2.1.1) and began screening for DR in the areas of Gwynedd, Ynys Mon and Blaenau Gwent in addition to the Bro Taf region in its first year of operation. Satellite centres were then opened in Caernarfon (North Wales) and Carmarthen (West Wales) (Figure 2.1.1)

Figure 2.1.1: DRSSW main base in Treforest, South Wales and location of satellite centres



The DRSSW had centralised administration and retinal grading at the Treforest base as well as hosting local photography teams (consisting of a photographer and a health care assistant [HCA]) for screening in South Wales (Figure 2.1.2). The two satellite centres provide a base for the North and West Wales photography teams. The DRSSW is a community based mobile screening service using both bespoke vans to transport equipment for screening to approximately 240 clinic venues (GP surgeries, hospital and community venues) as well two large dedicated screening vans to facilitate screening in remote locations or where access to adequate NHS facilities is difficult (Figure 2.1.3). In 2006, screening became available to the last remaining region of Wales i.e. Monmouth and all 100,000 eligible persons (at that time) were offered a screening appointment by the end of 2006. Therefore screening for DR for all 162,291 eligible persons (numbers correct in May 2012) with diabetes in Wales has been provided by the DRSSW since 2006.

Figure 2.1.2: DRSSW main base in Treforest, South Wales A) administration department B) grading department during the study period 2005-2009

A)



**Administration:
Appointments staff**



Administration :Scheduling staff (10) Call and recall system – ‘robust’

Appointment letters dispatched :

Location and date choices

Two appointments only given

Attendance/DNA list sent to GP

Calls per day 300-500

01.12.06-28.02.07 ~20,000 calls

Results sent to : Patient, GP, Diabetologist & Ophthalmologist

Figure 2.1.2 B: continued



Diabetic Retinopathy Graders (16)

Chief Grader (1)

Senior Grader (1) - Myself

Graders (14)

Training schedule :

6 week initiation course

18 month to final grade level

Diploma in Retinal Screening (C & G)

Quality Assurance QA :

Monthly

Professional body :

British Association of Retinal Screeners (BARS)

Figure 2.1.3: Two modes of mobile screening, 1) small vans to transport equipment to clinics and 2) the dedicated mobile screening unit.

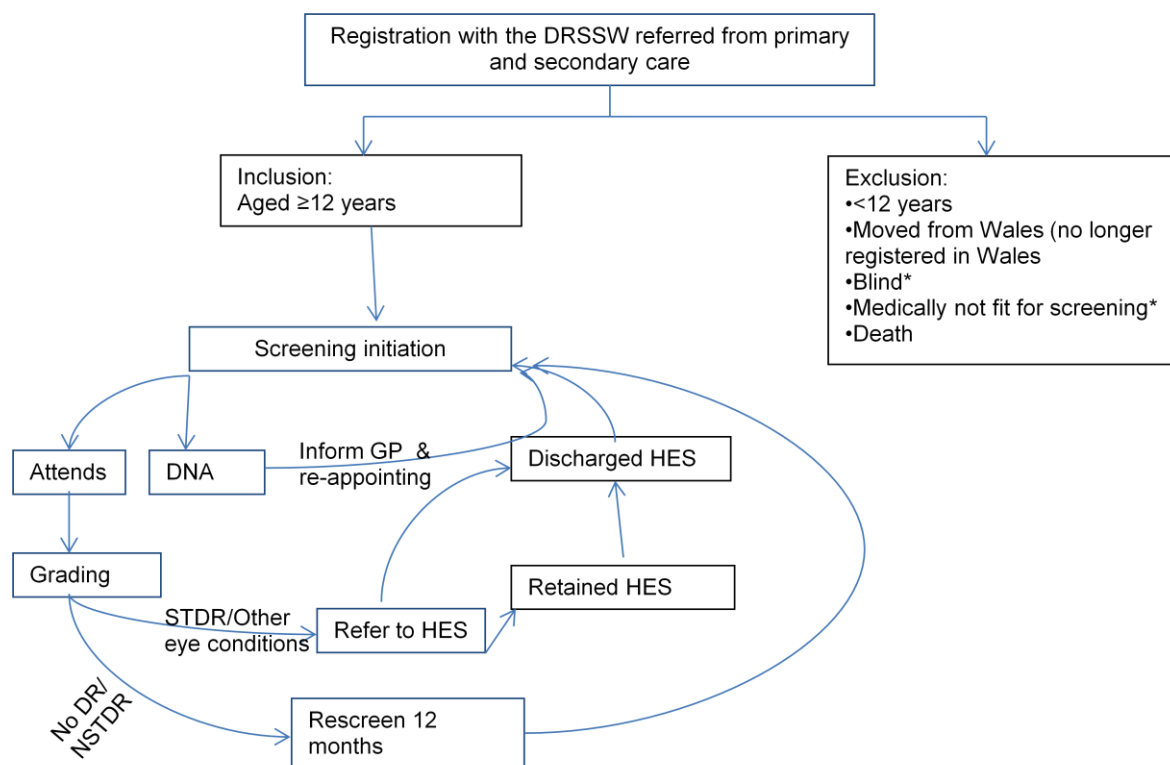


Organisation of screening

The procedure for screening was initiated following referral predominantly from primary care (GPs), but also from secondary care (hospital based services). All persons registered with a GP in Wales with diabetes aged 12 years and over were entitled to be referred to the DRSSW. Exclusions from screening included those under the age of 12 years, under the care of hospital eye service for DR, registered blind and without the perception of light in both eyes, medical reasons as determined by the persons GP or clinical director of the DRSSW for reasons such as terminal illness or where screening may cause harm etc and those who did not wish to participate in screening. Referrals were required to contain demographic details including: name, address, date of birth, date of diagnosis of diabetes, type of diabetes and current diabetes treatment. Unfortunately very often the information received from primary care was incomplete (see section 2.2.1 for details). The

procedures involving registration call and recall of persons for screening at the DRSSW are illustrated in Figure 2.1.4.

Figure 2.1.4 The Registration, call and recall process.



Key: DNA - Did not attend appointment; HES - Hospital eye services; STDR - Sight-threatening DR; DR - Diabetic retinopathy; GP - General practitioner; NSTDR - Non sight-threatening DR; *Exclusion from screening decided by persons GP.

The DR screening clinics were organised by administrators at the Treforest base who would send out appointments, and later dispatched the results to the patients, GPs, and where applicable the hospital based clinicians (at diabetic clinics). Once the location and timing of the screening clinics were confirmed, the photography teams, would be assigned to each clinic. At the clinics, a HCA would confirm the personal details, take a brief eye health history and obtain consent for each of the following: instillation of mydriatic eye drops, photography (lens and retina), grading and the use of the images for teaching and research. The HCA then tested the current/habitual visual acuity using a 3 meter illuminated Snellen chart, (with or

without the use of distance glasses). If this was worse than 6/9 a pinhole visual acuity measurement was then undertaken, followed by the administration of mydriatic eye drops (1.0% tropicamide). After approximately 15-20 minutes, to allow for pupil dilation, digital retinal images were taken by the photographer. Two standard 45° retinal images (one macular and one nasal field) per eye were taken (Figure 2.1.5).

Figure 2.1.5: Example of 2 x 45° retinal images (macula centred and nasal) taken per eye as standard by the DRSSW



Additional images were captured during the appointment if the photographer felt more information was required, such as a better view of peripheral lesions or external images, if images were of poor quality. All images were then stored on the photographer's laptop and downloaded onto the main server in Treforest at the end of each day/or week depending on the photographers schedule and location. Images were transmitted across secure NHS lines from the remote centres to the server at Treforest. All images are retained on the central server at Treforest for a minimum of eight years.

Training

All staff within the DRSSW participate in an initial 6 week internal training programme consisting of: lectures on diabetes, epidemiology, pathophysiology and the natural history of diabetic retinopathy, the anatomy of the eye, an introduction to the grading process, an introduction to retinal photography as well as administrative matters such as standard operating procedures. Once the generic (6 week) training programme is complete staff undergo further intensive departmental training. The further training involves a shadowing process: where photographers attended clinics and graders and administrators observed senior team members in base.

Photographers receive an intensive course on camera use and maintenance and must complete a portfolio of 50 patients before being allowed to take reduced clinics alone. Graders undergo an 18 month training process with monthly quality assurance. Once quality assurance confirmed staff were competent to grade images without lesions they move up to the next level of the grading protocol until at the end of the 18 month training process they are competent to refer cases into ophthalmology and participate in secondary grading. All staff are also required to complete the City and Guilds diploma in retinal screening.

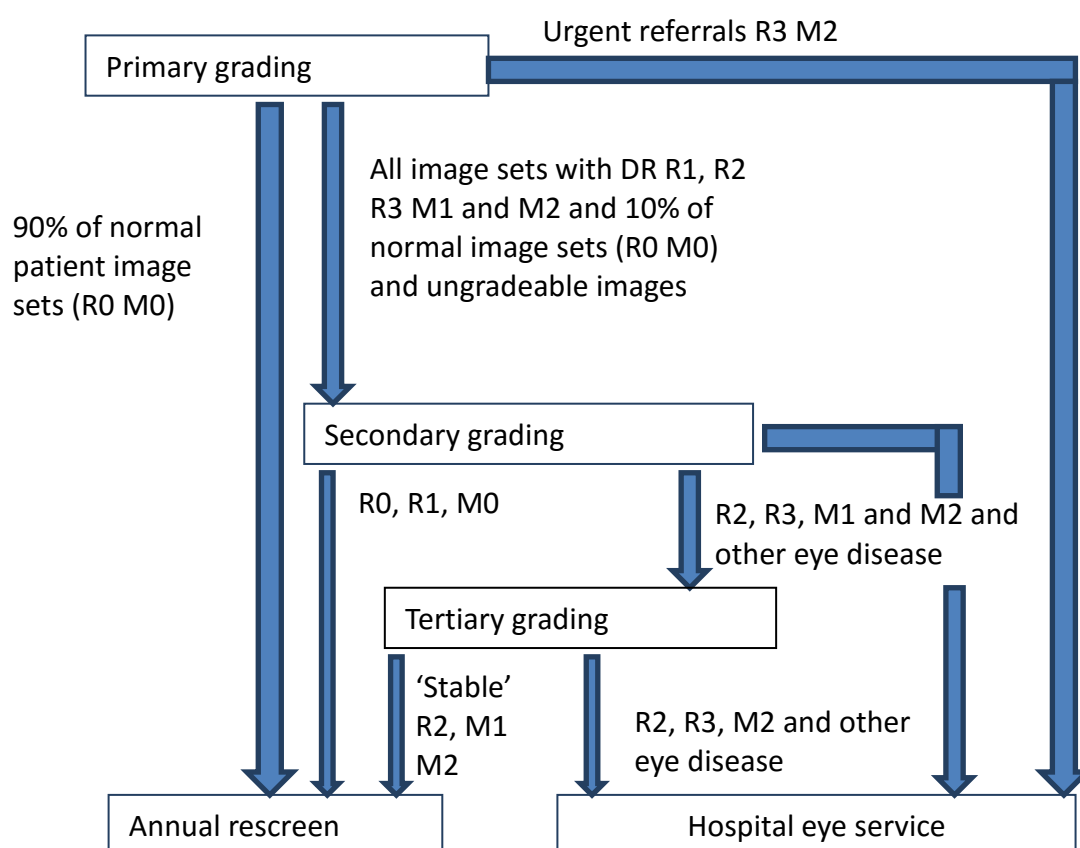
2.1.2.2 Evolution of Grading

The grading process 2003-2008

The DRSSW was launched in 2002, and utilised the same grading process as the Bro-Taf DRSS. The process involved checking the images in order to prioritise those images with sight-threatening conditions. These cases were seen first by the central grading staff so that if necessary, appointments could be arranged at the nearest HES as soon as possible. In some cases where HRC were present, images were graded and referred to HES the same day. All other retinal images were graded in date order. The grader would perform a full disease assessment

firstly of the right eye followed by the left eye using the DRSSW grading protocol, this initial grading would constitute the primary grading event. Following primary grading all images with disease identified (DR and other lesions), 10% of images without DR and ungradeable images underwent a secondary grading event. Secondary grading was carried out by a more senior grading team member where the grading was either finalised, or sent for tertiary grading. The tertiary grading event was conducted by an ophthalmologist, or the Clinical Director of the DRSSW for cases of sight threatening lesions such as PPDR or worse, or where maculopathy or other eye disease were present. This grading process for the period of 2003-2008 is represented in figure 2.1.6.

Figure 2.1.6: Grading process 2003-2008

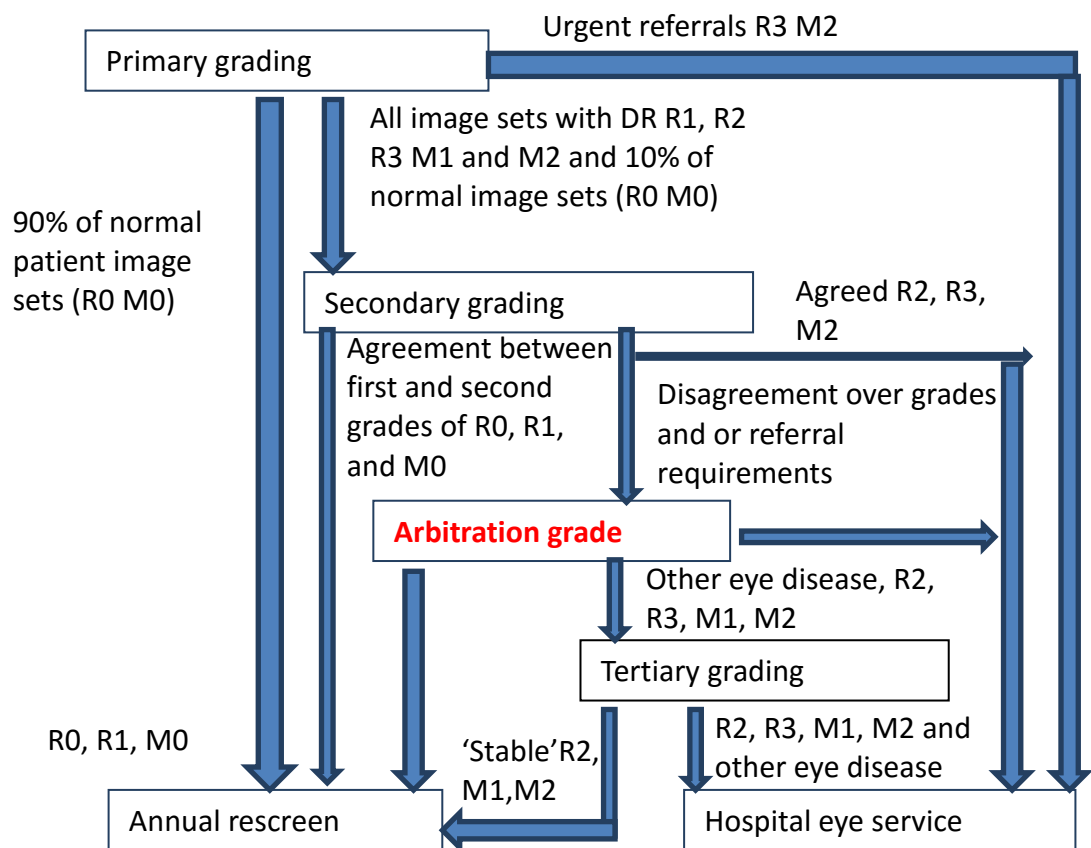


Stable R2, M1, M2 consists of lesions which have either been seen in HES previously and determined to be stable or when current images were compared to previous images lesions were determined to be unchanged

The grading process 2008 to the present day

The grading process was amended in 2008, to include an arbitration grading stage (Figure 2.1.7). Primary grading still involved a full disease assessment, with all screen positive cases and 10% of all screen negative cases being sent for secondary grading. Any disagreements between primary and secondary grading then undergo arbitration grading, by a more senior grader. Referral for tertiary grading occurs for the same reasons as previously mentioned. All ungradeable images are second graded and then referred to HES for further assessment.

Figure 2.1.7: Grading process 2008 to the present day



Stable R2, M1, M2 consists of lesions which have either been seen in HES previously and determined to be stable or when current images were compared to previous images lesions were determined to be unchanged.

Outcome of grading

Outcomes of grading were rescreen in 12 months, rescreen in 3 months (in the case of technical failures) or refer to HES. If the outcome was refer to HES the timescales were as follows: routine 3-6 months, soon 4-6 weeks, urgent 2-4 weeks and emergency within 2 weeks. The outcome was dependant on the final grade of DR and is detailed in Table 2.1.2.

Table 2.1.2: Grading outcomes from the DRSSW

DR grading	Meaning of grade	Outcome
R0 M0	No DR	Routine 12 month rescreen
R1.1 M0	Minimal BDR	
R1.2 M0	Moderate BDR	
R1.1 M1	Mild BDR with possible maculopathy	
R1.2 M1	Moderate BDR with possible maculopathy	
R2 M0	PPDR	Routine/soon referral to HES
R2 M1	PPDR	
R1.1 M2	Minimal BDR with definite maculopathy	
R1.2 M2	Moderate BDR with definite maculopathy	
R2 M2	PPDR with definite maculopathy	Soon referral to HES
R3 M0	PDR	Urgent referral to HES
R3 M1	PDR	
R1/2/3 M2	Any DR with exudative maculopathy and signs of oedema	
R3 M0/1/2	PDR with/without maculopathy but pre-retinal or vitreous Hm present	Emergency referral to HES

No DR - no diabetic retinopathy; BDR - background diabetic retinopathy; PPDR - pre-proliferative diabetic retinopathy; PDR - proliferative diabetic retinopathy; Hm - haemorrhage; HES - hospital eye service

2.1.2.3 Quality assurance

All departments at the DRSSW i.e. administration, photography and grading are subject to internal quality assurance (QA). There was regular monthly monitoring of

the call/recall system, validation of GP lists, monitoring of the quality of images taken by photographers as well as monitoring of the graders' competence (Table 2.1.3). All internal QA systems are ongoing and supported by continuous training.

Table 2.1.3: Grading monthly QA form

Primary grader						
Secondary grader		R0	R1.1	R1.2	R2	R3
	R0					
	R1.1					
	R1.2					
	R2					
	R3					

Blue denotes complete agreement between primary and secondary graders; above/below would indicate under or over grading by primary grader; sensitivities, specificities and positive predictive values are calculated based on this cross tabulation

External Quality Assurance (EQA) of the DRSSW is provided by the UK National Diabetic Eye Screening Programme with visits taking place once every three years. The EQA team consisted of a member from public health, a clinical lead (ophthalmologist, diabetologist, optometrist), a programme manager and a screening/grading reviewer. The visits assessed the programme based on whether or not it is meeting the minimum clinical standards.

2.1.3 Screening for DR in South Africa

Outside the UK screening for DR has been adopted using a variety of different models of delivery and sophistication depending on the availability of ophthalmologists, the technology for screening and funding.(Klein et al. 1985, Kristinsson et al. 1995, Agardh et al. 2011, Murthy et al. 2012, Olafsdottir et al.

2013) However, many countries remain without screening or have limited and rudimentary programmes available. This is especially true of developing nations where there are other pressures on their scarce financial resources. (Vashist et al. 2011, Khandekar 2012, Murthy et al. 2012, Burgess et al. 2013, Ramasamy et al. 2013)

In South Africa, screening for DR at the primary care level is almost nonexistent,(Seggie 2014) despite guidelines recommending annual screening since 2002, and the country joining the World Health Organisation (WHO) and International Agency for the Prevention of Blindness (IAPB) vision 2020 programme.(Department of Health 2002) Where it does exist it is conducted on an adhoc and opportunistic basis by a range of healthcare workers.(Cook et al. 2014) Although previous feasibility studies found that screening could increase fundal examinations by 42%, approximately 40% of those screened would require referral to already overstretched ophthalmology departments.(Mash et al. 2007)

2.1.3.1 Centre for Diabetes and Endocrinology, Johannesburg South Africa

Whilst screening for DR in the public sector in South Africa still faces many challenges, a diabetes management programme with annual screening for DR has been operational in the private sector since 1994, by the Centre for Diabetes and Endocrinology (CDE), Johannesburg (Figure 2.1.8).(Distiller et al. 2010) The CDE has a network of 262 smaller centres providing care to urban, rural and under-developed communities in South Africa. The programme is paid for by medical aid schemes and has more 18,000 persons with diabetes registered. The centre

utilises a trained multidisciplinary team of healthcare workers, including doctors specifically trained in diabetes management.

Figure 2.1.8 Map of South Africa



The CDE operates a diabetes management programme for the treatment and management of diabetes, and prevention of its complications. All persons with diabetes enrolled in the programme are entitled to a minimum standard of care as set out in Table 2.1.4.(Distiller et al. 2010)

All affiliated centres use a customized internet-based clinical management programme, which stores all patient contacts, findings, medication dispensed and laboratory results.(Distiller et al. 2010) This facility is used to check patient and centre compliance with the adopted 'Minimum Care Guidelines'. In addition, there is a full-time medical practitioner who conducts an ongoing peer review and audit of the centres annually.

Table 2.1.4: Minimum care standards within the CDE for persons with diabetes

Service Description	Frequency
Consultations:	
Doctor	x 2 annually
Nurse educator	x 2 annually
Nutritionist	x1 annually
Podiatrist	x 1 annually (screening)
DR screening	x 1 annually
Exercise physiologist	If required
Clinical psychologist	If required
Laboratory tests HbA _{1c}	x 2 annually (minimum)
Lipid profile	x 1 annually (minimum)
Renal function, microalbuminuria, eGFR	x 1 annually (minimum)
Full blood count	x 1 annually (minimum)
Blood Pressure	x 2 annually
24-h emergency line for community management of diabetes emergencies and advice	24/7/365
All diabetes medications and monitoring equipment	As prescribed
Insulin	As prescribed
Oral glucose-lowering agents	As prescribed
Blood glucose meters and test strips	As prescribed
Glucagon hypoglycaemia kit (insulin therapy_	replaced on use/expiry)
Ketone test strips (type 1 diabetes)	replaced on use/expiry)
Syringes, needles, lancets	As prescribed
Risk assumption for the costs of hospital admission	Acute diabetes emergencies only

eGFR - estimated glomerular filtration rate ; 24-h - 24 hour; DR - diabetic retinopathy

The HbA_{1c} assays are undertaken at one of four locally available commercial laboratories. The method used involves high-performance liquid chromatography, and the reference normal ranges for all laboratories were the same at 4.8–6.0%. Non-fasting lipid levels (total cholesterol, LDL-cholesterol, HDL-cholesterol and

triglycerides) are analysed by enzymatic methods using automated techniques.(Distiller et al. 2010) For any person, the same laboratory is used for follow-up purpose.

2.1.3.2 Screening for DR within the CDE

All persons with diabetes attending the CDE undergo routine digital retinal photography performed at the time of their first visit and annually thereafter. Digital retinal photography is conducted in a darkened room using a non-mydratic (NM) digital camera (Canon CR6–45NM) capturing one 45° macular centred image per eye without the use of mydriasis. The photography is undertaken by one of two trained technicians, one of whom was a diabetes nurse educator. All retinal images were graded at the time by a physician according to the CDE's own grading protocol. Table 2.1.5 compares the South African and DRSSW grading protocols.

Table 2.1.5: DRSSW and South Africa's grading protocols

DRSSW		South Africa	
Grade	Interpretation	Grade	Interpretation
R0	No DR	0	No DR
R1.1	Mild BDR < 5 Mas > 1 DD from fovea < 4 Hms > 1 DD from fovea 3 Mas < 1 DD from fovea exudates > 2 DD from fovea with or without CWS (< 5)	1	< 5 Ma / Hm
R1.2	Moderate BDR ≥ 5 Mas > 1 DD from fovea ≥ 4 < 8 Hms > 1DD from fovea per eye > 3 Mas < 1 DD from fovea with VA > 6/12 Circinate or grouped Ex > 2 DD from fovea but within arcades Questionable IRMA only in the presence of Ma/Hm	2	> 5 Ma / Hm
		3	Grade 2 plus hard Ex
		4	Grade 3 plus deep Hm
R2	Severe BDR (PPDR/NPDR) ≥ 8 blot Hm <i>per eye</i> Venous irregularities, beading, reduplication, venous loops (but not on their own) Definite IRMA with or without CWS (but not CWS on their own)	5	Grade 4 plus CWS or IRMA or venous beading
R3	PDR/ADED NVD NVE Pre-retinal Hm Vitreous Hm Pre-retinal fibrosis Traction retinal detachment	6	Neovascularisation Pre-retinal Hm &/ vitreous Hm
		7	Retinal detachment / rubeosis iridis
		8	not assessable due to small pupils / dense cataracts etc.
		9	not gradable/ lesions not due to DR
		10	blind due to DR
Maculopathy			
M0	No Maculopathy	present if hard exudates are within 1DD of the macula	
M1	Possible Maculopathy Ex < 2 DD >1DD from fovea > 3 Mas <1 DD from fovea with VA worse then 6/12 Hm < 2DD from fovea with VA worse then 6/12		
M2	Definite Maculopathy Ex <1dd from fovea		

No DR - no diabetic retinopathy; BDR - background diabetic retinopathy; PPDR - pre-proliferative diabetic retinopathy; PDR - proliferative diabetic retinopathy; ADED - advanced diabetic eye disease; NPDR - non-proliferative diabetic retinopathy; Ma - microaneurysm; Hm - haemorrhage; Ex - exudate; IRMA - intra-retinal microvascular abnormalities; CWS - cotton wool spots; DD - disc diameter;

2.2 Data cleaning

2.2.1 Diabetic retinopathy screening service for Wales DRSSW

For the purpose of this study information for the time period 2005 to 2009 was extracted from the DRSSW database by the software company Digital Healthcare. Although the DRSSW had been operational since 2003, during 2004 there was a slight change in grading protocol. Therefore only screening events taking place post 2005 were utilised for this study as the quality of the data prior to 2005 was uncertain. All data analysis was conducted in SPSS version 16 and Excel 2007.

During the data cleaning and validation process several inconsistencies in the data were noted. These included unrecorded, or even changes in type of diabetes over time, unrecorded date of diagnosis of diabetes, as well as an 'unrealistic' age at diagnosis of diabetes for the type of diabetes recorded e.g. 50% of persons with a diagnosis of type 1 diabetes had an age at diagnosis of 30 years or more. Whilst it is known that type 1 diabetes can manifest later on these cases are generally considered to be exceptions and need to be confirmed by GPs. Therefore, in order to ensure the integrity of the analysis a number of exclusion criteria were imposed on the dataset, resulting in 43,759 persons being excluded out of a total of 135,152. These exclusions were:

- Type of diabetes not recorded, n=29,807
- Type 1 diabetes with an age at diagnosis of 30 years or more, n=3,105,
However 730 of these were retained in the study for reasons detailed below
- Type 2 diabetes with an age at diagnosis of less than 30 years, n=10,847

The cut off age of 30 years at diagnosis of diabetes was proposed as it has been used in previous large scale epidemiological studies and clinical trials. (Klein et al. 1985, Kohner et al. 1998) Of the 3,105 persons with type 1 diabetes and an age at diagnosis of ≥ 30 years, 1,412 (45.5%) did not have evidence of DR at first screening. In order to minimise the number of persons with type 1 diabetes excluded from the analysis, the GPs were contacted and asked to confirm type of diabetes, and date of diagnosis of diabetes for these 1,412 persons. This resulted in 51.7% (730) being confirmed as having type 1 diabetes by their GP with an age at diagnosis of ≥ 30 years and therefore included in the subsequent analysis. 12.2% (172) were confirmed as having type 2 diabetes, whilst the remaining 36.1% (510) remained without a diagnosis of diabetes as the GP practice would not confirm type of diabetes over the telephone. Those persons originally classified as type 1 diabetes and subsequently confirmed as type 2 diabetes by GPs were excluded from the analysis.

2.2.2 Centre for diabetes and endocrinology, Johannesburg South Africa

Data from the CDE in South Africa was stored on an access database and anonymised before being transferred to us. All images were graded at the CDE by a physician in charge of the persons care using the CDE standardised grading protocol. Due to the differences between the CDE and DRSSW protocols (Table 2.1.5) it was necessary to re classify the images graded by the CDE as having DR according to the DRSSW protocol. All images were independently reviewed and re-graded by myself or one of two senior retinal graders using the DRSSW grading protocol. All persons originally graded as having no DR were not re-graded as this level of grading was the same in the South African and DRSSW grading protocols.

A total of 1,895 people required re-classifying as they had evidence of DR on retinal images, however images for 183 people were not available for this process and were therefore excluded from the dataset. Therefore 1,712 images were re-classified using the DRSSW grading protocol and a random sample of 123 (7.2%) images (n=238 eyes) underwent secondary grading by a second grader blinded to the results of the first grader to check agreement.

There was complete agreement between first and second grader for the grade of any DR in 75.2% (n=179 eyes) (Table 2.2.1) and maculopathy in 82.4% (n=196 eyes) (Table 2.2.2). Disagreement between the first and second grader occurred most commonly in retinopathy grades R1.2 and R2 with disagreement in 9.2% of cases or in 22 eyes. For maculopathy grades the most common disagreements were between M1 and M2 in 8.0% or 19 eyes. There were 2 cases where a large disagreement in grades occurred. In the first a retinal vein occlusion was present in the left eye which resulted in the first grader providing a grade of R0 M0 and the second grader giving R3 M2. As this finding was not due to DR or maculopathy the grade R0 M0 was retained. In the second vascular collaterals were present on the optic disc of the left eye, the first grader gave a grade of R3 M0 and the second grader gave a grade of R1.2 M0. Therefore, as the new vessels graded by the first grader were collaterals the second grader grades were retained. The inter-observer agreement level as assessed by Cohen's Kappa score for DR was moderate at 58.5% and substantial at 72% for maculopathy. There was a very good level of sensitivity for both DR at 96.8% and maculopathy at 93.8%. However, specificity was slightly below the Exeter standards for DR at 61.9% for DR and maculopathy at 86.2%.(British Diabetic Association 1997) Where the disagreements occurred an arbitration grade was performed, on a total of 59 eyes, by the author and was taken as the final grade.

Table 2.2.1: Level of agreement between the first and second grader for DR

	Grader 2					
	R0	R1.1	R1.2	R2	R3	Total
Grader 1	R0	13 (5.5%)	3 (1.3%)	3 (1.3%)	1 (0.4%)	20
	R1.1	6 (2.5%)	17 (7.1%)	7 (2.9%)	0	30
	R1.2	2 (0.8%)	11 (4.6%)	120 (50.4%)	20 (8.4%)	153
	R2	0	0	2 (0.8%)	20 (8.4%)	23
	R3	0	0	1 (0.4%)	2 (0.8%)	12
	Total	21	31	133	43	238

Kappa score 58.5%, sensitivity 96.8%, specificity 61.9%

Table 2.2.2: Level of agreement between the first and second grader for maculopathy

	Grader 2			
	M0	M1	M2	Total
Grader 1	M0	94 (39.5%)	5 (2.1%)	3 (1.3%)
	M1	11 (4.6%)	25 (10.5%)	1 (0.4%)
	M2	4 (1.7%)	18 (7.6%)	77 (32.4%)
	Total	109	48	81

kappa score 72.0%, sensitivity 93.8%, specificity 86.2%

2.3 Study populations

2.3.1 Diabetic retinopathy screening service for Wales

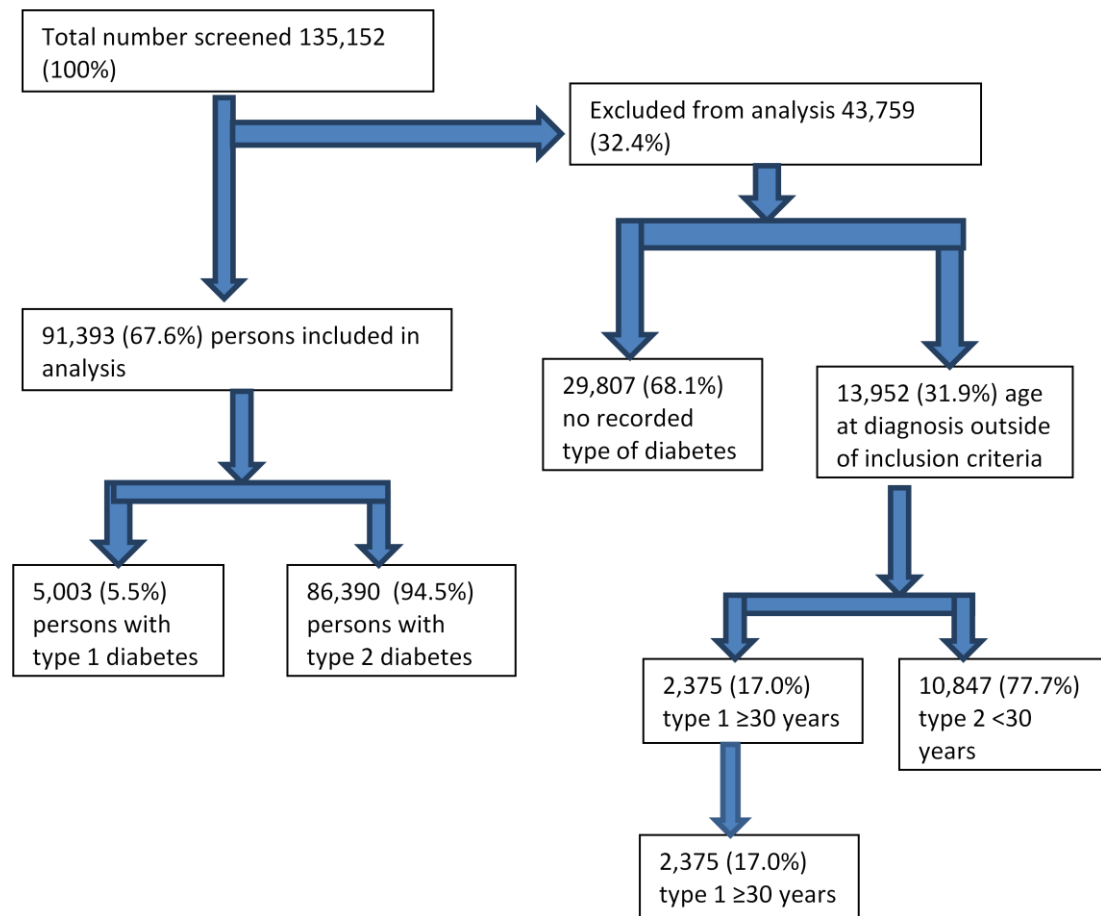
In Wales in 2012, the prevalence of diabetes was approximately 5.9% (2012).

Around 8.4% of people with diabetes in Wales during the study period were ineligible for screening for a variety of reasons including: 1.5% medical conditions/co-morbidities, 0.2% registered blind, 0.2% under the age of 12 years and 6.5% already being under the care of an ophthalmologist for DR. Therefore, 91.6% of persons with diabetes were eligible for screening. However,

approximately 20% failed to attend their DR screening appointments. Only details on those persons who attended screening were available for analysis, therefore, further analysis relating to missed appointments could not be undertaken. If for instance a person attended their first appointment, missed the second but attended the third appointment then the first appointment became their first screening event and the third appointment their second screening event.

From January 2005 to November 2009, 91,393 persons over the age of 12 years underwent screening for DR by the DRSSW and met the inclusion criteria stated in section 2.2.1 (Figure 2.3.1). 5.5% had type 1 diabetes and 94.5% had type 2 diabetes. Ethnicity data was not collected by the DRSSW at the time, and so was not available for analysis in this population. However, the majority of persons in Wales are Caucasian (95.6%), with 2.3% Asian, 0.6% Black and 1.5% other or mixed ethnic groups.(Office of National Statistics 2012)

Figure 2.3.1: Flow chart of inclusions and exclusions



2.3.2 Centre for diabetes and endocrinology Johannesburg, South Africa

South Africa has a population of more than 50.6 million the majority of whom are indigenous Africans (79.5%) with approximately 9% Caucasian, 9% Mixed Race and 2.5% Indian/Asian.(U.S. Department of State 2011) The prevalence of diabetes in South Africa has been estimated at 5-10%, amounting to 2.5-5.1 million people.(Mash et al. 2007) Approximately 18,000 of these were under the care of one of the CDE centres. Our study population came from the CDE centre based in Johannesburg.

The 5,565 subjects who had DR screening at the CDE in Johannesburg between 2001 and 2010 represent only 0.1%-0.2% of the total population estimated with diabetes in South Africa. The study population consisted of 71.2% Caucasians, 12.7% Indigenous Africans, 12.3% Indian Asians and 3.8% of Mixed race. As the majority of the population in South Africa are Indigenous African, the population attending the CDE in Johannesburg is therefore not representative of the total population of South Africa. In the study population the majority of persons had type 2 diabetes (71.5%) with 27.6% having type 1 diabetes. The remaining 0.9% with other forms of diabetes such as LADA and pre-diabetes/ impaired glucose tolerance (IGT), were excluded from all analysis. Subjects included in this analysis were classified as having type 1 (1,537) or type 2 (3,978) diabetes according to the American Diabetes Association classification of diabetes.(American Diabetes Association 2010)

2.3.3 Classification of DR employed in the study

Levels of DR were classified as no DR if no lesions were detected, any DR when at least one microaneurysm and/or a blot haemorrhage were detected, background DR (BDR), when microaneurysms or haemorrhages or exudates were present which did not require referral to HES i.e. DR grades R1.1, R1.2 and maculopathy grade M1. RDR, included PPDR (R2), and PDR (R3) as well as exudative maculopathy (M2). RDR is the level at which further assessment by an ophthalmologist at HES is deemed necessary for both the DRSSW and CDE populations. Grades were per person and based on the grade provided for the worst eye.

2.3.4 Classification of visual impairment and blindness

The classification of visual impairment and blindness is based on the best recorded level of visual acuity in the better seeing eye. The definition of normal vision, visual impairment and blindness was taken from the World Health Organisations criteria (World Health Organisation 2010) shown in Table 2.3.1

Table 2.3.1: Classification of normal vision, visual impairment and blindness from WHO's definition and as applied in this thesis.

WHO classification				Study			
0 Mild or no visual impairment	Equal to or better than	Log mar 0.3	Snellen 6/18	Normal vision	Equal to or better than	Log mar 0.60	Snellen 3/12
1 Moderate Visual impairment	Worse than	0.3	6/18	Visual impairment		0.78	3/18 to 3/36
2 Severe visual impairment	Worse than Equal to or better than	0.1 1.3	6/60, 3/60				
3 Blindness	Worse than	1.3,	3/60,	Blindness	Equal to or worse than	1.3	3/60 or worse
4 Blindness	Equal to or better than	0.02	CF				
5 Blindness	better than or equal to light perception	0.02	CF				
6	No Light perception Undetermined or unspecified						

2.5 Aims

- To estimate the prevalence and incidence of DR within two distinct populations of persons undergoing systematic screening for the presence of DR based in Wales, UK, and Johannesburg, South Africa.
- To investigate the risk factors associated with the prevalence and incidence of DR.
- To investigate the incidence of referable DR within defined subgroups of persons with type 1 and type 2 diabetes in order to elucidate low risk groups, in which the screening interval could be safely extended.
- To estimate the prevalence of visual impairment and blindness within the DRSSW and CDE programs.

2.6 Statistical analysis

Statistical analysis of the DRSSW and CDE datasets were conducted separately. Prevalence of any DR, BDR and RDR was determined at first screening and the incidence of any DR, BDR and RDR over the course of the study were calculated in persons without evidence of DR at first screening using survival functions obtained from Kaplan Meier analysis. The continuous data throughout this thesis were summarised by mean \pm standard deviation, (SD) when the data was normally distributed and by median and interquartile range (IQR) if not normally distributed. Normality was checked using q-q plots. Categorical data were presented as total numbers (n) and percentage (%). The Student's t-test was used to compare the means of two groups and analysis of variance (ANOVA) to compare the mean of more than two groups for normally distributed continuous data. Whereas Mann-Whitney U and Kruskal Wallis tests were used for non-normally distributed continuous variables. Pearson chi-squared test was used for categorical data. P

values of <0.05 were taken as statistically significant. Although extensive numbers of tests were performed, they were used only as an indication of differences between sub-groups for the identification of possible important explanatory variables which, in conjunction with univariate regression methods, yield a smaller subset of variables for multivariable analysis. Therefore, adjustment for multiple comparisons was not necessary.

Regression modelling was used to identify important risk factors for the development of DR. Where the data was cross-sectional, outcomes were modelled using logistic regression analysis. Longitudinal data was modelled using survival analysis, by fitting Cox proportional hazards models. All estimates were accompanied by 95% confidence intervals (95% CI).

Logistic regression analyses used in this thesis are common in medical research and were used to assess risk factors for the presence or absence of DR. Odds ratios with 95% CI were used to denote the likelihood of an event occurring. An odds ratio equal to one occurs when the odds are the same in two groups and is equivalent to no association between the exposure and the disease.(Kirkwood et al. 2003). Odds ratios (OR) less than one are interpreted as the event being less likely to occur for an increase in the predictor variable, whereas odds ratios larger than one are interpreted as the event being more likely to occur.

Survival analysis used allowed the exploration of the time to an event of interest and in this thesis was the time to the first occurrence of DR – any DR, background DR (BDR) and referable DR (RDR).(Benitez-Parejo et al. 2011) The Kaplan-Meier

estimate was used as this method avoids the assumption that individuals lost to follow up are censored half way through the interval. The hypothesis, that the ratio of the hazard functions between two groups are the same, was tested using the log-rank test.

Cox proportional hazards regression was used to estimate the effect of defined risk factors on the incidence of any DR, BDR and RDR i.e. age at diagnosis; duration of diabetes; treatment of type 2 diabetes and gender in the DRSSW population and age at diagnosis; duration of diabetes; gender; HbA_{1c} and hypertension in the CDE population. The proportional hazards model assumes that the ratio of the hazards comparing different exposure groups remains constant over time relative to the hazard. The proportional hazard model is the most general of the regression models because it is not based on any assumptions concerning the nature or shape of the underlying survival distribution. (Kirkwood et al. 2003) A key reason for the popularity of the Cox model is that even though the baseline hazard is not specified, good estimates of regression coefficients, hazard ratios and adjusted survival curves can be obtained for a wide variety of data situations. Therefore, the Cox model is robust and its results would closely approximate the results for the correct parametric model.

The variables available for analysis in the DRSSW population were age, gender, age at diagnosis of diabetes, duration of diabetes, type of diabetes and treatment of diabetes. Within the CDE population the variables available for analysis were age, gender, age at diagnosis of diabetes, duration of diabetes, type of diabetes, ethnicity, HbA_{1c}, the presence of hypertension, total cholesterol level,

albumin:creatinine ratio, use of ACE inhibitors and aspirin, and the patients smoking history.

For regression models, continuous data, i.e. age at diagnosis, duration of diabetes, HbA_{1c} etc, were categorised to avoid assumptions of linearity. The groups were separated into tertiles or quartiles for type 1 and type 2 diabetes separately to ensure an equal distribution. The variables were sub-grouped for each analysis and are detailed in table 2.6.1. In this thesis all variables, both time-independent and time-dependent, were assessed at entry into both the DRSSW and CDE programmes and therefore treated as time-independent variables.

Table 2.6.1: Details of subgroups of continuous variables

	T1DM	T2DM
	DRSSW Chapter 3	
Duration of diabetes (years)	<10 years 10-19 years ≥20 years	<5 years 5-9 years ≥10 years
Age at diagnosis (years)	<10 years 11-20 years 21-29 years	≤55 years 56-65 years ≥65 years
	Chapter 4	
Duration of diabetes (years)	≤10 years 11-19 years ≥20 years	<5 years 5-9 years ≥10 years
Age at diagnosis (years)	≤10 years 11-20 years >20 years	30-49 years 50-59 years 60-69 years ≥70 years
	CDE chapter 5	
Total Chol (mmol/L)	Low <5 High >5	<5 >5
ACR (mg/mmol)	Low <3 High >3	<3 >3
HbA _{1c} (%)	<7 7.0 -7.9 8.0-8.9 >9	<6.6 6.6-7.4 7.5 -8.9 >9
Duration of diabetes (years)	<7 7-15 >15	<3 3-8 (1,360) >8 (1,224)
Age at diagnosis (years)	<14 14-26 >26	<46 (1,403) 46-55 (1,265) >55 (1,286)
	Chapter 6	
Total Chol (mmol/L)	≤4.43 4.44-5.38 ≥5.39	<4.90 ≥4.90
ACR (mg/mmol)	Low <3 High >3	
HbA _{1c} (%)	≤7.4 7.41-8.9 >8.9	≤6.7 6.71-7.8 >7.8
Duration of diabetes (years)	≤5 6-11 ≥12	<5 5-10 >10
Age at diagnosis (years)	≤12 13-22 23-33 ≥34	<45 45-50 51-60 >60

Chapter 3

Prevalence of diabetic retinopathy, visual impairment and associated risk factors at first screening -Diabetic Retinopathy Screening Service for Wales, 2005-2009

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3.1 Introduction

DR continues to be an important microvascular complication in both type 1 and type 2 diabetes. Previous findings suggests that DR is evident in approximately 84% of persons with type 1 diabetes of 40 years duration and advanced DR in 50%.(Hammes et al. 2011) In contrast, about 12-19% (Looker et al. 2012, Olafsdottir et al. 2013) of persons with type 2 diabetes have some DR already at the time of diagnosis,(Kohner et al. 1998) with 4% developing PDR after 20 years or more of diabetes.(Olafsdottir et al. 2013)

Wales currently has a population of approximately 3.1 million, predominantly Caucasian, with the majority situated in the industrial south (~60%) with the remainder of the country generally regarded as rural.(Welsh Government 2012) In 2003 the Welsh government commissioned the DRSSW, which became an all Wales service at the end of 2006 when it was in a position to offer DR screening appointments to all eligible persons in Wales (see Chapter 2). In 2012 there were 177,238 (5.9%) persons with diabetes in Wales known to the DRSSW of whom, 162,291 (91.6%) were eligible for annual screening. Approximately 8.4% of persons with diabetes in Wales were ineligible for screening for a variety of reasons including: medical (1.5%), blindness (0.2%), under the age of 12 years (0.2%) and being under the care of a HES (ophthalmology) (6.5%). Therefore, 91.6% of persons with diabetes were eligible for screening, of whom approximately 20% unfortunately did not attend their allotted appointments.

The prevalence of DR has previously been described for several populations,(Zhang et al. 2010, Yau et al. 2012) using different methods for the

detection and also differing criteria for classifying DR which accounts in part for the broad variations observed (Table 3.1.1).

Table 3.1.1: Studies of the prevalence of DR worldwide.

Study	N	Recruit ment	Inclusions	Exclusions	Other details	Prevalence of DR
WESDR 1984(Klein et al. 1984a)	1,210 identified 996 included	1979- 1980	<30 years using insulin eligible	under 30 years at diagnosis of diabetes, confined to nursing, home, died, did not have diabetes, Moved and gestational diabetes	7 standard stereoscopic colour fundus photographs per eye following mydriasis. Grading performed using the ETDRS adaption of the Airlie house classification	No DR 29% Any DR 70% NSTDR 48% STDR 22%
WESDR 1984(Klein et al. 1984b)	5,431 identified 1,780 included 696 non-insulin users and 674 insulin users Random selection from each group included in the study 576/2,341 duration of diabetes 0-4yrs 579/2,465 duration of diabetes 5-14yrs All 625 duration of diabetes ≥15yrs Total included 1,780	1979- 1980	≥30 years at diagnosis of diabetes. diagnosis of diabetes by GP confirmed by random or postprandial glucose of at least 200mg/dl (11.1mmol/l) or fasting glucose 140mg/dl (7.8mmol/l) on 2 occasions and residence in the area.	Exclusions as above	Photography and grading as above	No DR 45.6% Non-insulin 60.9%, Insulin 29.8% Any DR 54%, Non-insulin 38.5%, insulin 70.1% NSTDR 44.8%, non- insulin 35.4%, insulin 54.5% STDR 9.3% non- insulin 3%, insulin 15.6%

Iceland 1994(Kristi nsson et al. 1994a)	298 identified 205 included (~90% of type 1 population in Iceland)	1989- 1990	Type 1 diabetes	some patient with type 1 diabetes of 0-5 years not yet referred to the clinic and some refuse to participate in screening.	Retinal examines are performed by ophthalmologists specialising in the retina using biomicroscopy with slit lamp and indirect ophthalmoscope following dilation. Iceland National grading protocol	Any DR 51.7% PDR 12.7%
Iceland 1994(Kristi nsson et al. 1994b)	245 identified 243 included (~1/5th of type 2 population in Iceland)	1989- 1990	Type 2 diabetes		As above	NDR 59% Any DR 41% PDR 7% DME10%
Liverpool 2002(Youni s et al. 2002)	10,440 invited for screening 1,050 type 1 diabetes and 9,390 type 2 diabetes 831 type 1 diabetes and 7,231 type 2 diabetes attended	1991- 1999	Type 1 diabetes with an age at diagnosis <30 years with insulin dependence of >30 years with evidence of ketoacidosis Type 2 diabetes age at diagnosis ≥30 years of <30years without insulin dependence.	approximately 800 pts under the care of ophthalmology	2 cameras canon CR4-45NM or Topcon TRC 50SX Images were 35mm film Grading protocol was an adaption of the ETDRS	NoDR Type 1 53.2% type 2 72.5% Any DR Type 1 45.7% Type 2 25.3% STED Type 1 16.4% Type 2 6.0% PDR Type 1 3.7% Type 2 0.5%

Norwich 2009(Misra et al. 2009)	20,788 people 205 possible type 1's included	1990- 2006	Type 2 diabetes	Those under the care of ophthalmology and type 1 diabetes	Canon 45NM following mydriasis Images captured on colour transparency film followed by digital images Grading performed by diabetologist, then ophthalmologist and finally trained graders Grading used European guidelines and then NSC	Any DR 25.3% STDR 0.6% STED 2.9%
USA 2010(Zhan g et al. 2010)	6,797 interviewed 1,006 included 795 previously diagnosed diabetes and 211 undiagnosed.	2005- 2008	Diabetes defined as self-report of previous diagnosis by a clinician or HbA1c $\geq 6.5\%$ People aged ≥ 40 years		Canon CR6- 45NM 2 images per eye not dilated Graded using the Airlie House classification system (ETDRS)	Any DR 28.5% VTDR 4.4%

Systematic review 2012(Yau et al. 2012)	35/58 identified studies included 22,896 people	1984-2010	Prevalence figures provided for 18-21 studies with similar definitions and methodologies All studies used retinal photography Grading performed using ETDRS, AAO, EURODIAB, UKNSCG, 21 Studies dilated pupils 4 photographed 1 eye only number of fields per eye taken were: single field: 6 2 fields: 16 3 fields: 2 4 fields:2 6 fields: 1 7 fields: 7 9 fields: 1 Ranging from 30-60°	Any DR 35.36% PDR 7.24% DME 7.48% VTDR 11.72%
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Looker 2012 (Looker et al. 2012)	51,526 persons with newly diagnosed type 2 diabetes identified. 47,090 were screened by before the end 2010. 43,523 had a gradeable result. Coverage approximately 99% of the total diabetic population in Scotland	2005- 2008	Those registered on Sci-dc database with type 2 diabetes data was extracted up until end of 2010.	Excluded those under the care of ophthalmology	Single fields per eye without mydriasis if images were unassessable then slit lamp biomicroscopy used however this data was not available for analysis. (approximately 1%).	Any DR 19.3% RDR 1.9% R3/4 0.7% Prevalence of any DR in those screened within a year of diagnosis was 18.3% RDR 1.6% and those screened more than 1 year after diagnosis was 20.5% and 2.3% and more than 2 years from diagnosis was 20.7% and 2.7%. Within 3 months of diagnosis was 18.5% and 1.4%.
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A systematic review by Yau et al (Yau et al. 2012) estimated the global prevalence of DR and determined the major associated risk factors in an individual participant analysis to by pooling a total 35 studies (22,896 people) with retinal photographs carried out between 1980 and 2008 in the USA, Australia, Europe and Asia. These studies included used a variety of different methods and media to obtain and grade retinal photographs: 35mm film and digital images, through dilated and undilated pupils capturing between one and nine fields per eye with a small minority photographing one eye only, with grading utilising the ETDRS scale, the American Academy of Ophthalmology International clinical diabetic retinopathy disease severity scale, or the UK National Screening Committee guidelines. The quoted overall prevalence of any DR in this analysis was 34.6% and vision threatening DR was 10.2%.. When confined to studies of similar methodologies the prevalence increased slightly to 35.4% (4,487/12,620) for any DR and 11.7% (1,481/12,710) vision threatening DR.

Our study (Thomas et al. 2014) of the prevalence of DR represents the largest community based national DR screening programme using standardised and quality assured image capture and grading methodologies (see chapter 2).

3.2 Aims

The primary aim of this study was:

- to determine the prevalence of any DR, BDR and RDR within the DRSSW based on each person's first screening visit

The secondary aims of this study were

- to investigate the impact of the currently available putative risk factors (duration of diabetes, age, treatment of type 2 diabetes and gender) on the prevalence of any DR, BDR and RDR
- to determine the prevalence of visual impairment and blindness within the DRSSW at first screening
- to investigate the impact of risk factors (DR status, duration of diabetes and age at screening) on the prevalence of visual impairment or blindness

3.3 Methods

The methods of screening, data cleaning and statistical analysis reported in this chapter are all described in detail in Chapter 2. In brief, the screening protocol included assessment of visual acuity (VA) using a 3 meter illuminated Snellen chart, followed by capture of 2x45° digital retinal images per eye (following mydriasis with 1% tropicamide) with a non-mydriatic Canon DGi camera. Grading was then performed by accredited retinal graders at a central grading centre using a standard grading protocol.

The inclusion criteria for this study was: 1) diagnosis of type 1 diabetes and an age at diagnosis of <30 years on insulin therapy 2) diagnosis of type 2 diabetes and an age at diagnosis of ≥30 years. In this chapter different variables (duration of diabetes, age at diagnosis of diabetes, treatment of type 2 diabetes and gender) were assessed for their relationship with the presence of any DR, BDR and RDR using binary univariate and backwards stepwise multivariate logistic regression analyses.

3.4 Results

From January 2005 to November 2009, 135,152 persons with diabetes over the age of 12 years underwent their first screening for DR with the DRSSW. However, 32.4% (43,759) were not eligible for further analysis as they did not meet the stated inclusion criteria (see above section 3.3). Of those excluded 29,807 (22.1%) did not have the type of diabetes recorded on their referral form and 13,952 (10.3%) had an age at diagnosis outside the stated limits for both type 1 and type 2 diabetes.

The remaining 67.6% (91,393) of the total population screened were eligible for inclusion of which 5.5% (5,003) had type 1 diabetes (T1DM) and 94.5% (86,390) had type 2 diabetes (T2DM). Table 3.4.1 shows that those who were excluded from the analysis had a slightly longer duration of diabetes (10.5 vs 6.0) with more using insulin (28.0 vs 14.6) and a higher prevalence of DR (35.7 vs 32.3) especially RDR (7.1 vs 5.0) compared to those included in the analysis.

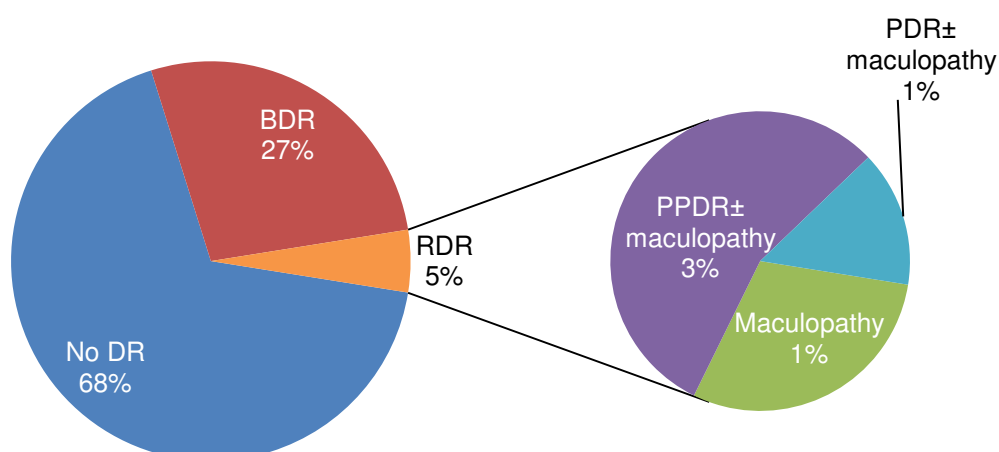
The overall prevalence of DR in those included in the analysis was 32.3% with 67.6% without any evidence of DR (Figure 3.4.1). Of the persons with DR, 27.3% had BDR and 5.0% had RDR. The RDR category consisted of 1.7% PPDR, 1.5% maculopathy, 1.1% PPDR with maculopathy, 0.4% PDR and 0.3% PDR with maculopathy (Table 3.4.1). Additionally 2.0% of the population had ungradeable images (percentage excluded from the total with/without DR).

Table 3.4.1: Characteristics and prevalence of DR within the whole population undergoing screening in Wales and those included in the analysis.

	Population excluded	Population included
N	43,759	91,393
Age yrs mean (SD)	61.1 (15.4)	63.7 (13.7)
Gender n (%):		
Male	23,568 (56.8)	51,211 (56.3)
Female	17,939 (43.2)	39,703 (43.7)
Age at diagnosis of diabetes yrs mean (SD)	49.6 (18.2)	57.8 (15.1)
Known duration of diabetes yrs mean (SD)	10.5 (10.2)	6.0 (6.8)
Treatment of diabetes n (%):		
Diet only	4,956 (27.5)	26,025 (28.8)
OHA	8,012 (44.5)	51,071 (56.5)
Insulin	5,042 (28.0)	13,229 (14.6)
Ungradeable images % (95% CI)	2.0 (0.9, 0.2)	2.0 (1.9, 2.1)
DR status: % (95% CI)		
No DR	64.3 (63.8, 64.7)	67.6 (67.3, 67.9)
Any DR	35.7 (35.3, 36.2)	32.3 (32.0, 32.6)
BDR	28.6 (28.2, 29.0)	27.3 (27.0, 27.6)
PPDR only	2.2 (2.1, 2.4)	1.7 (1.6, 1.8)
Maculopathy (with BDR)	2.0 (1.8, 2.1)	1.5 (1.5, 1.6)
PPDR with maculopathy	1.6 (1.4, 1.7)	1.1 (1.0, 1.2)
PDR only	0.8 (0.7, 0.9)	0.4 (0.4, 0.5)
PDR with maculopathy	0.6 (0.5, 0.7)	0.3 (0.3, 0.3)
RDR	7.1 (6.9, 7.4)	5.0 (4.9, 5.1)

Key: yrs - years; SD – Standard deviation; n – number; OHA – oral hypoglycaemic agents; DR – diabetic retinopathy; 95 % CI – 95% confidence intervals; BDR – Background diabetic retinopathy; PPDR – pre-proliferative diabetic retinopathy; PDR – Proliferative diabetic retinopathy

Figure 3.4.1: Overall prevalence of DR in the study population



No DR - No diabetic retinopathy; BDR - Background diabetic retinopathy; RDR - Referable diabetic retinopathy; PPDR - Pre-proliferative diabetic retinopathy; PDR - proliferative diabetic retinopathy

3.4.1 Diabetic retinopathy

3.4.1.1 T2DM

3.4.1.1.1 Prevalence of DR

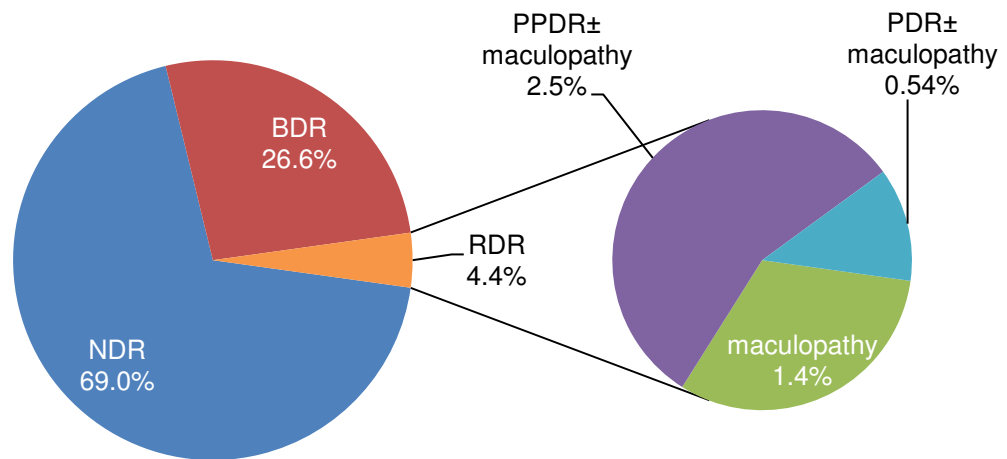
The population of persons with T2DM (86,390) undergoing screening for the first time at the DRSSW had a mean age of 65.3 years, a known duration of diabetes (median) of 4 years and a mean age of 60.0 years at diagnosis of diabetes (Table 3.4.2). The majority of persons were male (56.4%), 30.5% were diet controlled, 59.9% were receiving OHAs whilst 9.5% were on insulin therapy. The prevalence of any DR was 31.0%, BDR was 26.6% and RDR was 4.4% (Figure 3.4.2).

Table 3.4.2: Characteristics and prevalence of DR in persons with T2DM undergoing screening for the first time at the DRSSW.

	T2DM (n = 86,390)
Age yrs mean (SD)	65.3 (11.7)
Gender n (%):	
Male	48,490 (56.4)
Female	37,446 (43.6)
Known duration of diabetes yrs median (IQR)	4.0 (1.0-7.0)
Treatment n (%):	
Diet only	26,025 (30.5)
OHA	51,071 (59.9)
Insulin	8,226 (9.5)
Age at diagnosis of diabetes mean yrs (SD)	60.0 (11.9)
Ungradeable images % (95% CI)	2.1 (2.0, 2.2)
DR status: % (95%CI)	
No DR	69.0 (68.7, 69.3)
Any DR	31.0 (30.7, 31.3)
BDR	26.6 (26.3, 26.9)
PPDR only	1.5 (1.4, 1.6)
Maculopathy (with BDR)	1.4 (1.3, 1.5)
PPDR with maculopathy	0.97 (0.91, 1.04)
PDR only	0.31 (0.28, 0.35)
PDR with maculopathy	0.23 (0.20, 0.27)
RDR	4.4 (4.3, 4.5)

n - number; yrs - years; SD - standard deviation; IQR - interquartile range; 95% CI - 95% confidence interval; BDR – background diabetic retinopathy; PPDR – pre-proliferative diabetic retinopathy; PDR - proliferative diabetic retinopathy

Figure 3.4.2 Prevalence of DR in persons with T2DM



Any DR – any diabetic retinopathy; BDR – background diabetic retinopathy; RDR – referable diabetic retinopathy; PPDR - preproliferative diabetic retinopathy; PDR - proliferative DR

3.4.1.1.2 Risk factors for DR

Known duration of diabetes

The median duration of diabetes for those noted to have any evidence of DR was 6 years, similar to those with BDR i.e. 5 years duration, although those with evidence of RDR had a longer duration of diabetes at 10 years (Table 3.4.3). Those persons without evidence of DR the median duration of diabetes was shorter at 3 years.

These differences between those with any DR, BDR and RDR compared to those without DR were significant. As expected due to the correlation with duration of diabetes age and age at diagnosis of diabetes were also significantly different for those with any DR, BDR and RDR compared to those without evidence of DR.

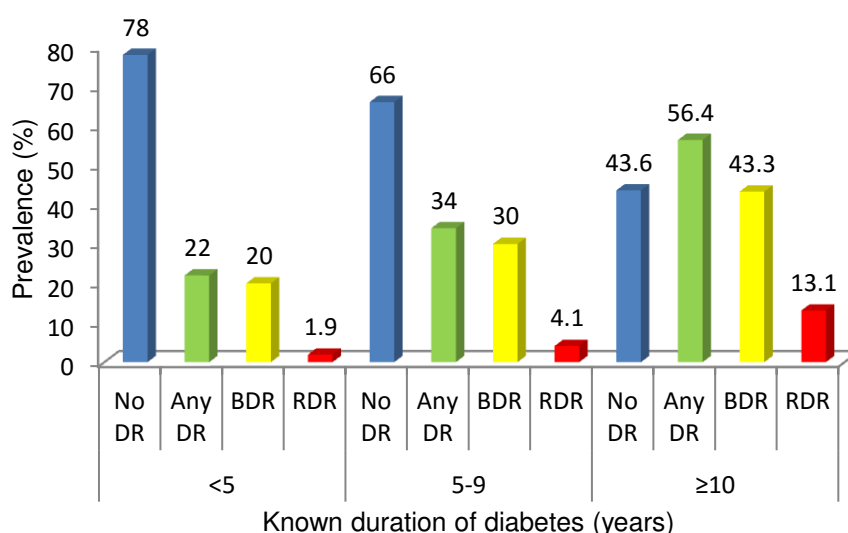
Table 3.4.3: Difference in characteristics for those persons with T2DM presenting without DR, with any DR, BDR or RDR

	No DR (n = 58,674)	Any DR (n = 26,216)	P value No DR vs. any DR	BDR (n = 22,482)	RDR (n = 3,734)	P value No DR vs. BDR and RDR
Age yrs mean (SD)	64.6 (11.7)	66.3 (11.4)	<0.001	66.5 (11.5)	65.1 (11.1)	<0.001
Sex: n (%)			<0.001			<0.001
Male	32,312 (55.4)	15,425 (59.1)		13,109 (58.6)	2,316 (62.1)	
Female	26,020 (44.6)	10,684 (40.9)		9,271 (41.4)	1,413 (37.9)	
Duration of diabetes yrs median (IQ)	3.0 (1.0-6.0)	6.0 (3.0-11.0)	<0.001	5.0 (2.0-10.0)	10.0 (5.0-15.0)	<0.001
Treatment of diabetes: n (%)			<0.001			<0.001
Diet	20,384 (35.2)	5,078 (19.6)		4,730 (21.3)	348 (9.4)	
OHA	33,585 (57.9)	16,446 (63.6)		14,210 (64.1)	2,236 (60.6)	
Insulin	4,012 (6.9)	4,339 (16.8)		3,232 (14.6)	1,107 (30.0)	
Age at diagnosis of diabetes yrs mean (SD)	60.3 (11.7)	58.7 (12.1)	<0.001	59.3 (11.9)	54.7 (12.1)	<0.001

NDR – no diabetic retinopathy; Any DR – any diabetic retinopathy; BDR – background diabetic retinopathy; RDR – referable diabetic retinopathy; yrs – years; SD – standard deviation; IQ – Interquartile range

The prevalence of DR increased with increasing known duration of diabetes (Figure 3.4.3). The prevalence of any DR increased from 22.0% in persons with diabetes for <5 years, to 34.0% in persons with diabetes for 5-9 years and 56.4% in persons with diabetes for ≥10 years. The prevalence of BDR increased similarly to any DR from 20.0% to 30.0% and 43.3% respectively. The prevalence of RDR increased by 11.2% from 1.9% in those with a duration of diabetes for <5 years to 13.1% in those with diabetes for ≥10 years.

Figure 3.4.3: Prevalence of diabetic retinopathy by duration of diabetes in persons with T2DM



Any DR – any diabetic retinopathy; BDR – background diabetic retinopathy; RDR – referable diabetic retinopathy;

Within the first two years of diagnosis of diabetes the prevalence of any DR and BDR was high at 20.3 and 18.6% respectively (Table 3.4.4). Whereas the prevalence of RDR was low within the first two years from diagnosis of diabetes at 1.7%. After a known duration of diabetes of ≥10 years half of those with diabetes had any DR (51.1%) 40.6% of which was BDR and 10.5% was RDR. After having diabetes for ≥25 years the prevalence of any DR was 68.5%, 47.3% of which was BDR and 21.2% was RDR.

Table 3.4.4: Percentage of any DR, BDR and RDR by increasing duration of diabetes in persons with T2DM.

Known duration of diabetes (yrs)	n	Any DR % (95% CI)	BDR % (95% CI)	RDR % (95% CI)
0-2	32,193	20.3 (19.9-20.7)	18.6 (18.2-19.1)	1.7 (1.5-1.8)
3-4	16,208	25.3 (24.6-26.0)	22.8 (22.2-23.5)	2.5 (2.2-2.7)
5-6	11,946	30.2 (29.4-31.0)	27.0 (26.2-27.8)	3.2 (2.9-3.6)
7-8	6,902	37.6 (36.5-38.8)	32.7 (31.6-33.8)	4.9 (4.4-5.4)
9-10	5,402	45.4 (44.1-46.8)	38.3 (37.0-39.6)	7.1 (6.5-7.8)
11-12	3,479	51.1 (49.4-52.7)	40.6 (38.9-42.2)	10.5 (9.5-11.6)
13-14	2,197	56.2 (54.1-58.3)	43.7 (41.6-45.8)	12.5 (11.2-14.0)
15-16	2,062	61.1 (59.0-63.2)	45.5 (43.4-47.7)	15.6 (14.1-17.3)
17-18	986	64.9 (61.9-67.8)	47.9 (44.8-51.0)	17.0 (14.8-19.5)
19-20	996	65.6 (62.6-68.5)	48.0 (44.9-51.1)	17.6 (15.3-20.1)
21-22	643	63.0 (59.2-66.6)	46.7 (42.8-50.5)	16.3 (13.7-19.4)
23-24	364	67.0 (62.1-71.7)	45.9 (40.8-51.0)	21.2 (17.3-25.6)
25-28	524	68.5 (64.4-72.3)	47.3 (43.1-51.6)	21.2 (17.9-24.9)
29+	533	67.4 (63.3-71.2)	49.2 (44.9-53.4)	18.2 (15.2-21.7)

Key: yrs - years; n – total number of persons; Any DR – any diabetic retinopathy; BDR – background diabetic retinopathy; RDR – referable diabetic retinopathy;; 95% CI – 95% confidence interval

In univariate logistic regression the presence of any DR was significantly associated with increasing known duration of diabetes i.e. known duration 5-9 years OR 1.83 and known duration ≥ 10 years OR 4.52 compared to a known duration of <5 years (Table 3.4.5). Similar associations were seen for the presence of BDR and known duration of diabetes i.e. 5-9 years OR 1.76, ≥ 10 years OR 3.81 compared to <5 years. The association of RDR with known duration of diabetes was even greater i.e. 5-9 years OR 2.49 and ≥ 10 years OR 11.96 compared to <5 years.

Table 3.4.5: Univariate logistic regression analysis for the risk factors associated with the presence of any DR, BDR and RDR in persons with T2DM

	Any DR OR (95%CI)	BDR OR (95%CI)	RDR OR (95%CI)
Age at diagnosis of diabetes (yrs):			
≤55 (n=30,184)	1.00	1.00	1.00
56-65 (n=26,912)	0.82 (0.79, 0.85)	0.87 (0.85, 0.92)	0.53 (0.49, 0.57)
≥66 (n=29,124)	0.75 (0.72, 0.77)	0.83 (0.80, 0.86)	0.38 (0.35, 0.41)
Male	1.16 (1.13, 1.20)	1.14 (1.10, 1.17)	1.32 (1.23, 1.41)
Duration of diabetes (yrs):			
<5 (n=49,390)	1.00	1.00	1.00
5-9 (n=21,592)	1.83 (1.77, 1.90)	1.77 (1.71, 1.84)	2.50 (2.28, 2.75)
≥10 (n=15,238)	4.59 (4.42, 4.77)	3.87 (3.71, 4.03)	12.14 (11.18, 13.19)

yrs - years; Any DR – any diabetic retinopathy; BDR – background diabetic retinopathy; RDR – referable diabetic retinopathy; OR - odds ratio; 95% CI - 95% confidence interval

In multivariate logistic regression analysis after adjusting for age at diagnosis of diabetes, gender and treatment of diabetes, the risk of RDR was 1.9- fold higher when known duration of diabetes was 5-9 years and 7.4-fold higher when the known duration of diabetes was ≥10 years when compared to those with diabetes duration <5 years (Table 3.4.6).

Table 3.4.6: Multivariate logistic regression analysis for the risk factors associated with the presence of any DR, BDR and RDR in persons with T2DM

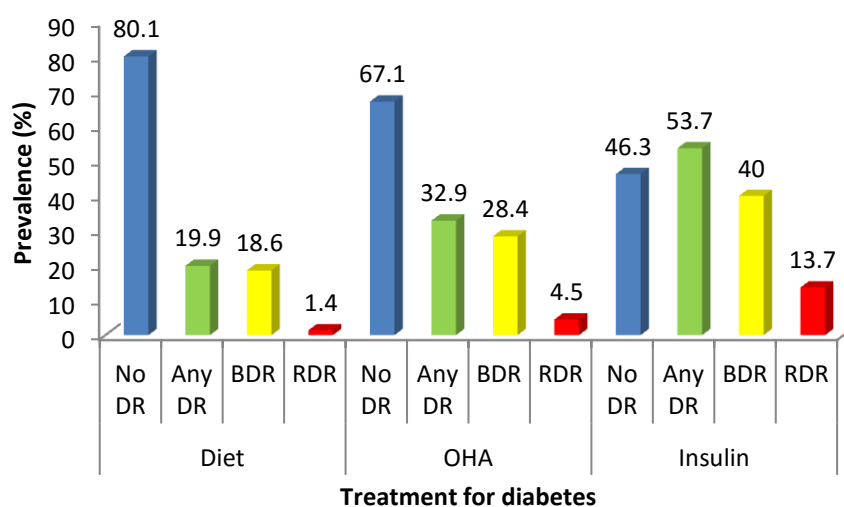
	Any DR OR (95%CI)	BDR OR (95%CI)	RDR OR (95%CI)
Age at diagnosis of diabetes (yrs):			
≤55 (n=30,184)	1.00	1.00	1.00
56-65 (n=26,912)	0.97 (0.94, 1.01)	1.01 (0.97, 1.06)	0.69 (0.63, 0.75)
≥66 (n=29,124)	1.16 (1.12, 1.21)	1.20 (1.15, 1.25)	0.81 (0.74, 0.89)
Male	1.17 (1.14, 1.21)	1.15 (1.11, 1.19)	1.30 (1.20, 1.39)
Duration of diabetes (yrs):			
<5 (n=49,390)	1.00	1.00	1.00
5-9 (n=21,592)	1.60 (1.54, 1.66)	1.58 (1.52, 1.64)	1.86 (1.69, 2.05)
≥10 (n=15,238)	3.70 (3.55, 3.86)	3.27 (3.13, 3.42)	7.43 (6.80, 8.13)

yrs - years; Any DR – any diabetic retinopathy; BDR – background diabetic retinopathy; RDR – referable diabetic retinopathy; OR - odds ratio; 95% CI - 95% confidence interval

Treatment of diabetes

The prevalence of DR increased as treatment of diabetes advanced from diet only, to OHA and eventually insulin therapy (Figure 3.4.4). The prevalence of BDR increased from 18.6% in persons treated by diet alone to 28.4% in those using OHAs and to 40.0% in those requiring the addition of insulin therapy. The prevalence of RDR was low in those treated by diet alone at 1.4% but increased to 4.5% in those requiring OHAs and 13.7% in persons on insulin therapy. These differences were significant (Table 3.4.3 pg 108)

Figure 3.4.4: Prevalence of DR by treatment of diabetes in persons with T2DM



Any DR – any diabetic retinopathy; BDR – background diabetic retinopathy; RDR – referable diabetic retinopathy; UG - ungradeable

The presence of any DR was significantly associated with OHA or insulin (OR 1.96, OR 4.34 respectively) therapy compared to diet alone (Table 3.4.7). Similar associations were seen for the presence of BDR i.e. treatment with OHA OR 1.82 or insulin OR 3.47 compared to diet alone. The presence of RDR was associated with the treatment of diabetes (OHA OR 3.90 and insulin OR 16.16 compared to diet alone).

Table 3.4.7 Univariate logistic regression for treatment of diabetes

	Any DR OR (95% CI)	BDR OR (95% CI)	RDR OR (95% CI)
Treatment of diabetes:			
Diet	1.00	1.00	1.00
OHA	1.97 (1.90, 2.04)	1.82 (1.76, 1.89)	3.90 (3.48, 4.37)
Insulin	4.65 (4.41, 4.91)	3.72 (3.51, 3.94)	17.32 (15.27, 19.63)

After adjusting for age at diagnosis, known duration of diabetes and gender persons on treatment with OHA and insulin therapies were at an increased risk of having any DR, BDR and RDR compared to those maintained on diet and lifestyle alone (Table 3.4.8). Those on treatment with OHA s had a 1.6- fold increased risk of having any DR, 1.5 fold increased risk of BDR and a 2.7-fold increased risk of RDR. Those on insulin therapy had an even greater risk at 2.7- and 2.4-fold for the presence of any DR and BDR respectively and a 6.9 fold increased risk of RDR.

Figure 3.4.8 Multivariate logistic regression analysis for treatment of diabetes adjusted for age at diagnosis, known duration of diabetes and gender.

	Any DR OR (95% CI)	BDR OR (95% CI)	RDR OR (95% CI)
Treatment of diabetes			
Diet	1.00	1.00	1.00
OHA	1.59 (1.53, 1.65)	1.52 (1.46, 1.58)	2.66 (2.36, 2.99)
Insulin	2.76 (2.60, 2.93)	2.41 (2.26, 2.56)	6.93 (6.05, 7.94)

3.4.1.1.3 Summary of main findings

- The prevalence of any DR was 31.0% in persons with T2DM, BDR was 26.6% and RDR was 4.4% at first screening event
- The presence of any DR, BDR and RDR within two years of diagnosis of type 2 diabetes was 20.3% 18.6% and 1.7% respectively increasing to 65.5%, 48.0% and 17.8% respectively after 20 years of known diabetes.
- Multivariate analysis indicated that those with a known duration of 10 years or more had a 3.7-fold increased risk of any DR and a 7.4 fold increased risk of RDR compared to those with diabetes of less than 10 years after adjusting for age at diagnosis, gender and treatment of diabetes.

- In multivariate analysis those requiring insulin therapy were at a 2.8-fold increased risk of any DR and a 6.9-fold increased risk of RDR compared to those on diet alone, after adjustment for age at diagnosis, gender and duration of diabetes.

3.4.1.2 T1DM

3.4.1.2.1 Prevalence of DR

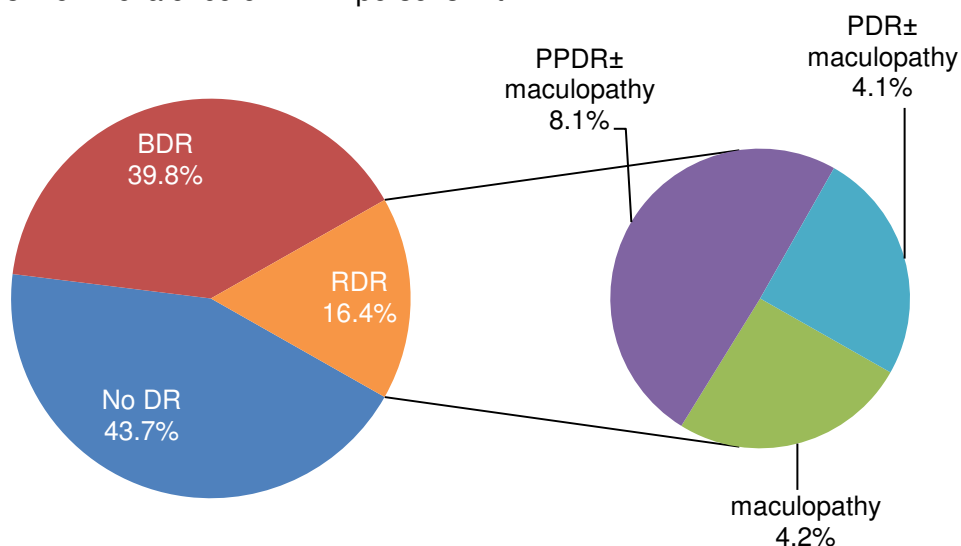
The characteristics and prevalence of DR of persons with T1DM is included in Table 3.4.9. The mean age was 36.5 years; median duration of diabetes 13.0 years, and mean age at diagnosis of diabetes was 19.7 years. The majority were male (54.7%) and all were receiving insulin therapy. The prevalence of any DR was 56.3%, BDR 39.8% and RDR 16.4% (Figure 3.4.5). The category of RDR consisted of 4.2% maculopathy only, 8.1% PPDR with or without maculopathy and 4.1% PDR with or without maculopathy.

Table 3.4.9: Characteristics at first screening in persons with T1DM

	T1DM (n = 5,003)
Age mean yrs mean (SD)	36.5 (16.4)
Gender n (%):	
Male	2,721 (54.7)
Female	2,257 (45.3)
Known duration of Diabetes yrs median (IQR)	13.0 (6.0-25.0)
Insulin n (%)	5,003 (100)
Age at diagnosis of diabetes yrs mean (SD)	19.7 (13.7)
Unassessable images % (95%CI)	0.5 (0.3, 0.7)
DR status: % (95%CI)	
No DR	43.7 (42.4, 45.1)
Any DR	56.3 (54.9, 57.7)
BDR	39.8 (38.4, 41.2)
PPDR only	5.2 (4.6, 5.9)
Maculopathy (with BDR)	4.2 (3.7, 4.8)
PPDR with maculopathy	2.9 (2.5, 3.4)
PDR only	2.6 (2.2, 3.1)
PDR with maculopathy	1.5 (1.2, 1.9)
RDR	16.4 (15.4, 17.4)

Key: yrs – years; SD – Standard deviation; n – number; IQR – Interquartile range; OHA – oral hypoglycaemic agents; DR – diabetic retinopathy; 95 % CI – 95% confidence intervals; BDR – Background diabetic retinopathy; PPDR – pre-proliferative diabetic retinopathy; PDR – Proliferative diabetic retinopathy

Figure 3.4.5: Prevalence of DR in persons with T1DM



No DR - No diabetic retinopathy; BDR - Background diabetic retinopathy; RDR - Referable diabetic retinopathy; PPDR - Pre-proliferative diabetic retinopathy; PDR - proliferative diabetic retinopathy

3.4.1.2.2 Risk factors and DR

Duration of Diabetes

The median duration of diabetes for those noted to have any DR was 21 years, similar to those with BDR at 19 years and RDR at 24 years (Table 3.4.10).

However for those persons without evidence of DR the median duration of diabetes was shorter at 6 years. The differences in duration of diabetes between those with any DR, BDR and RDR compared to those without DR were highly significant. The mean age at diagnosis for those persons noted to have any DR on first screening was 15.5 years, which was similar to those presenting with BDR at 15.9 years and RDR at 14.6 years and were much younger than those present with the same in T2DM at 58.7, 59.3 and 54.7 years respectively. Those presenting without any signs of DR were significantly older at diagnosis of diabetes with a mean age of 25.2 years compared to those with any DR, BDR and RDR. .

Table 3.4.10: Difference in characteristics for those persons with T1DM presenting without DR (NDR), any DR, BDR or RDR.

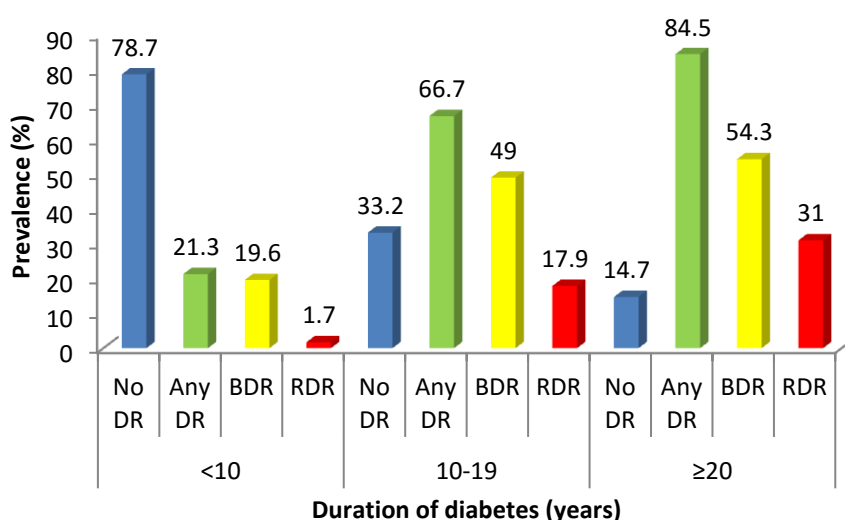
	No DR (n = 2,181)	Any DR (n = 2,802)	P value No DR vs. any DR	BDR (n = 1,983)	RDR (n = 819)	P value No DR vs. BDR and RDR
Age yrs mean (SD)	34.6 (19.2)	37.9 (13.5)	<0.001	37.3 (14.3)	39.3 (11.2)	<0.001
Sex: n (%)			0.904			<0.001
Male	1,183 (54.5)	1,524 (54.7)		1,015 (51.5)	509 (62.4)	
Female	988 (45.5)	1,264 (45.3)		957 (46.5)	307 (37.5)	
Duration of diabetes yrs median (IQ)	6.0 (3.0-12.0)	21.0 (13.0-31.0)	<0.001	19.0 (11.0- 30.0)	24.0 (17.0-31.0)	<0.001
Age at diagnosis of diabetes yrs mean (SD)	25.2 (17.2)	15.5 (7.9)	<0.001	15.9 (7.9)	14.6 (7.8)	<0.001

yrs - years; No DR – no diabetic retinopathy; Any DR – any diabetic retinopathy; BDR – background diabetic retinopathy; RDR – referable diabetic retinopathy; yrs – years; SD – standard deviation; IQ – Interquartile range

The prevalence of DR increased with increasing duration of diabetes (Figure 3.4.6).

The prevalence of any DR increased from 21.3% in persons with a duration of diabetes <10 years to 66.7% in those with a duration of 10-19 years and to 84.5% in those with a duration of ≥20 years.

Figure 3.4.6: Prevalence of diabetic retinopathy by duration of diabetes in persons with T1DM



NDR - No diabetic retinopathy; BDR - Background diabetic retinopathy; RDR - Referable diabetic retinopathy

In persons with diabetes for less than 2 years the prevalence of any DR, BDR and RDR was 9.7% 9.0% and 0.7% respectively (Table 3.4.9). This increased to 47.2% with any DR, 40.5% BDR and 6.7% RDR in those with diabetes for 9-10 years. In those with diabetes for 19-20 years this was further increased to 78.5% with any DR, 46.4% BDR and 32.1% RDR.

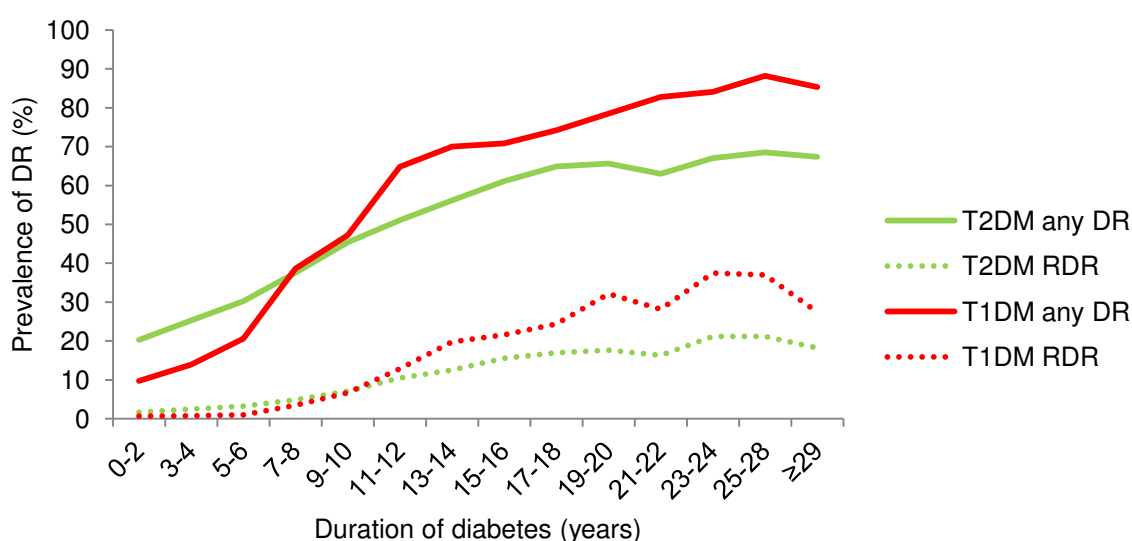
Table 3.4.11: Percentage of any DR, BDR and RDR by increasing duration of T1DM.

Duration of diabetes (yrs)	n	Any DR % (95% CI)	BDR % (95% CI)	RDR % (95% CI)
0-2	588	9.7 (7.6-12.4)	9.0 (7.0-11.6)	0.68 (0.26-0.17)
3-4	390	13.9 (10.8-17.6)	13.1 (10.1-16.8)	0.77 (0.26-2.2)
5-6	389	20.6 (16.9-24.9)	19.5 (15.9-23.8)	1.0 (0.40-2.6)
7-8	345	38.6 (33.6-43.8)	35.1 (30.2-40.3)	3.5 (2.0-6.0)
9-10	343	47.2 (42.0-52.5)	40.5 (35.5-45.8)	6.7 (4.5-9.9)
11-12	318	64.8 (59.4-69.8)	51.9 (46.4-57.3)	12.9 (9.7-17.0)
13-14	273	70.0 (64.3-75.1)	50.2 (44.3-56.1)	19.8 (15.5-24.9)
15-16	250	70.8 (64.9-76.1)	49.2 (43.1-55.4)	21.6 (17.0-27.1)
17-18	213	74.2 (67.9-79.6)	49.8 (43.1-56.4)	24.4 (19.1-30.6)
19-20	209	78.5 (72.4-83.5)	46.4 (39.8-53.2)	32.1 (26.1-38.7)
21-22	174	82.8 (76.5-87.7)	54.6 (47.2-61.8)	28.2 (22.0-35.3)
23-24	176	84.1 (78.0-88.8)	46.6 (39.4-54.0)	37.5 (30.7-44.9)
25-28	322	88.2 (84.2-91.3)	51.2 (45.8-56.7)	37.0 (31.9-42.4)
29+	989	85.3 (83.0-87.4)	57.9 (54.8-61.0)	27.4 (24.7-30.3)

Key yrs - years; n – total number of persons; Any DR – any diabetic retinopathy; BDR – background diabetic retinopathy; RDR – referable diabetic retinopathy; 95% CI – 95% confidence interval

The prevalence of any DR was lower within the first 2 years of diagnosis in persons with T1DM compared to those with T2DM at 9.7% vs. 20.3% (Figure 3.4.7). After a duration of diabetes of 6 years the prevalence of any DR in persons with T2DM increased at a more constant rate until a known duration of 18 years. Following this the prevalence rate reached a plateau. In contrast the prevalence of any DR rapidly increased for those persons with T1DM until a duration of 12 years after which the prevalence of any DR continued to increase but at a slower rate. There was a low prevalence of RDR in both T2DM and T1DM during the first 6 years following the diagnosis of diabetes (3.2% vs. 1.0%). After a duration of 6 years the prevalence of RDR increased for both T2DM and T1DM although the increase was more rapid for T1DM

Figure 3.4.7: Prevalence of DR in both persons with T2DM and T1DM.



Duration of diabetes was stratified into tertiles for purposes of the logistic regression analysis which were: <10 years (reference), 10-19 years and ≥ 20 years. The univariate logistic regression is represented in Table 3.4.12, the presence of any DR was seen to be significantly associated with increasing duration of diabetes: 10-19 years (OR 7.4) and ≥ 20 years (OR 21.3) compared to <10 years diabetes duration. This was similar for the presence of BDR with duration of diabetes of 10-19 years (OR 5.9) and >20 years (OR 14.7). This association was even stronger for the presence of RDR for those persons with duration of diabetes of 10-19 years (OR 24.7) and those with diabetes ≥ 20 years (OR 96.3) when compared to those with diabetes for <10 years.

In the multivariate analysis following adjustment for age at diagnosis and gender, duration of diabetes remained strongly associated with the presence of any DR and BDR increasing further for RDR (Table 3.4.13). Those persons with a duration of diabetes of 10-19 years had a 28.9-fold increased risk of RDR and those with diabetes for ≥ 20 years had a 100.8-fold increased risk compared to those with a duration of diabetes of <10 years.

Table 3.4.12: Univariate logistic regression analysis for the risk factors associated with the presence of any DR, BDR and RDR in persons with T1DM

	Any DR OR (95%CI)	BDR OR (95%CI)	RDR OR (95%CI)
Age at diagnosis of diabetes (yrs):			
≤10 (n=1,278)	1.00	1.00	1.00
11-20 (n=1,711)	0.97 (0.83, 1.13)	1.03 (0.87, 1.21)	0.85 (0.70, 1.04)
≥21 (n=2,014)	0.40 (0.35, 0.47)	0.46 (0.39, 0.54)	0.30 (0.24, 0.37)
Male	1.01 (0.90, 1.13)	0.88 (0.78, 1.00)	1.38 (1.17, 1.63)
Duration of diabetes (yrs)			
<10 (n=1,876)	1.00	1.00	1.00
10-19 (n=1,341)	7.43 (6.34, 8.71)	5.92 (5.02, 6.99)	24.78 (16.88, 36.37)
≥20 (n=1,786)	21.43 (18.04, 25.45)	14.84 (12.41, 17.73)	97.02 (66.35, 141.88)

yrs - years; Any DR – any diabetic retinopathy; BDR – background diabetic retinopathy; RDR – referable diabetic retinopathy; OR - odds ratio; n - number; 95% CI - 95% confidence interval

Table 3.4.13: Multivariate logistic regression analysis for the risk factors associated with the presence of any DR, BDR and RDR in persons with T1DM

	Any DR OR (95%CI)	BDR OR (95%CI)	RDR OR (95%CI)
Age at diagnosis of diabetes (yrs):			
≤10 (n=1,278)	1.00	1.00	1.00
11-20 (n=1,711)	1.33 (1.10, 1.60)	1.32 (1.09, 1.60)	1.34 (1.02, 1.76)
≥21 (n=2,014)	0.54 (0.45, 0.64)	0.55 (0.46, 0.66)	0.40 (0.31, 0.52)
Male	1.17 (1.02, 1.35)	1.09 (0.95, 1.27)	1.86 (1.50, 2.32)
Duration of diabetes (yrs)			
<10 (n=1,876)	1.00	1.00	1.00
10-19 (n=1,341)	7.89 (6.69, 9.31)	6.28 (5.29, 7.47)	28.92 (19.52, 42.86)
≥20 (n=1,786)	21.12 (17.71, 25.20)	14.93 (12.43, 17.93)	100.75 (68.27, 148.68)

yrs - years; Any DR – any diabetic retinopathy; BDR – background diabetic retinopathy; RDR – referable diabetic retinopathy; OR - odds ratio; n - number; 95% CI - 95% confidence interval

3.4.1.2.3 Summary of main findings

- In persons with T1DM at first screening the prevalence of any DR was 56.2%, BDR 39.8% and RDR was 16.4%
- After 20 years or more of diabetes 78.5% had evidence of DR and 32.1% RDR
- After adjusting for age at diagnosis and gender those with T1DM for 20 years or more had approximately a 20- fold increased risk of any DR and a 100-fold increased risk of RDR compared to those with diabetes of less than 10 years duration.

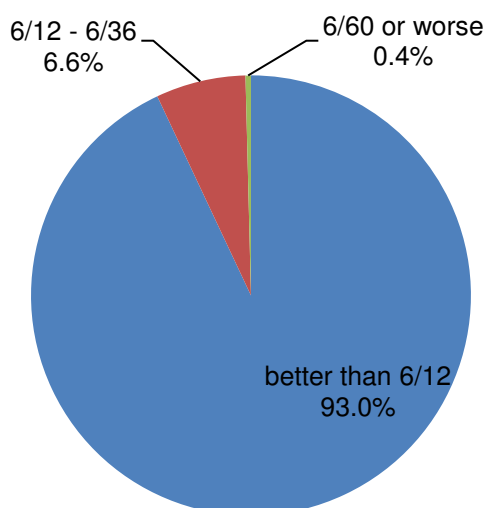
3.4.2 Visual acuity

3.4.2.1 T2DM

3.4.2.1.1 Prevalence of visual impairment and blindness

The majority (93.0%) of persons had normal vision (better than 6/12) in their better eye at first screening (Figure 3.4.8). 6.6% had visual impairment (6/12-6/36) and 0.4% were blind (6/60 or worse).

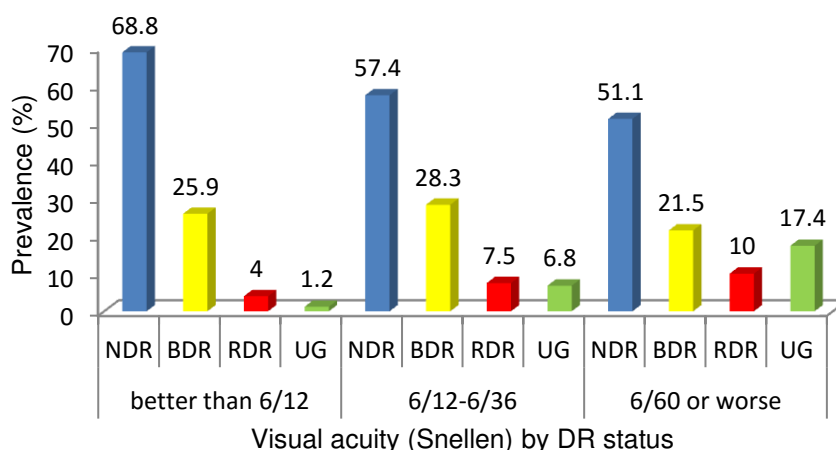
Figure 3.4.8: Visual acuity in persons with T2DM at first screening



The prevalence of no DR decreased as visual acuity worsened (Figure 3.4.9), with the prevalence of no DR decreasing from 69% in those with normal vision to 57% in those with visual impairment and 51.1% in those who were blind. The prevalence of BDR remained similar across the levels of vision, whereas the prevalence of RDR and the number of ungradeable images increased with worsening vision. The prevalence of RDR increased from 4% in those with normal vision to 7.5% in those with visual impairment and 10% in those who were categorised as blind. The

frequency of ungradeable images increased from 1% in those with normal vision to 7% and 17% in those with visual impairment and blindness respectively.

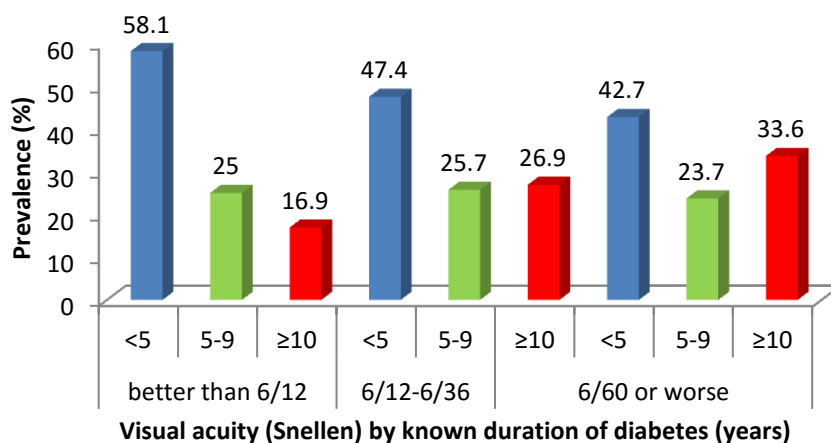
Figure 3.4.9: Visual acuity by DR level in persons with T2DM



Any DR – any diabetic retinopathy; BDR – background diabetic retinopathy; RDR – referable diabetic retinopathy; UG - ungradeable

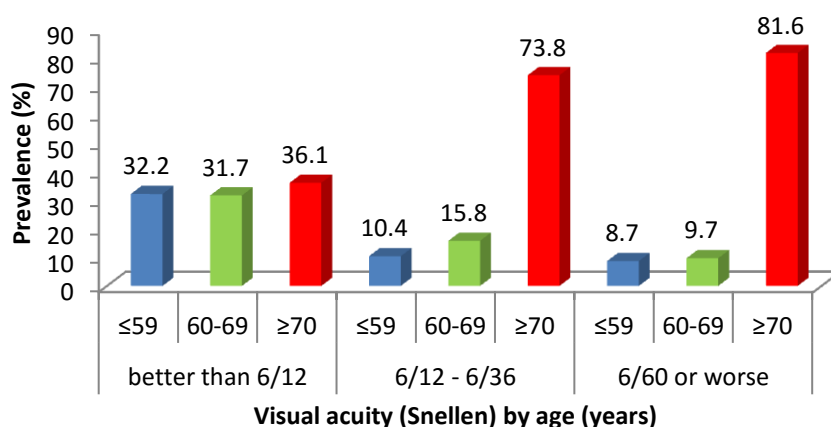
In those persons with a known duration of < 5 years the prevalence of normal vision was 58%, visual impairment was 47% and those categorised as blind was 43% (Figure 3.4.10). In contrast the proportion of persons with a known duration of diabetes of ≥10 years 17% had normal vision, 27% visual impairment and 34% in those who were categorised as blind.

Figure 3.4.10: Visual acuity by duration of diabetes in persons with T2DM



The number of persons with normal vision was evenly distributed across the different age groups (Figure 3.4.11). Of those persons with visual impairment and blindness the majority were aged ≥ 70 years at screening (74% and 82% respectively).

Figure 3.4.11: Prevalence of visual acuity by age



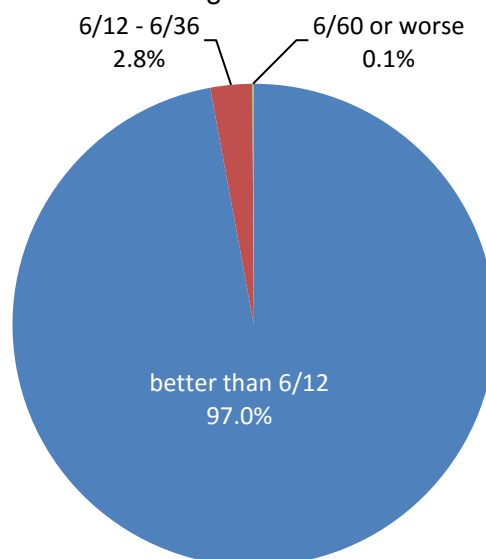
Any DR – any diabetic retinopathy; BDR – background diabetic retinopathy; RDR – referable diabetic retinopathy; UG - ungradeable

3.4.2.2 T1DM

3.4.2.2.1 Prevalence of visual impairment and blindness

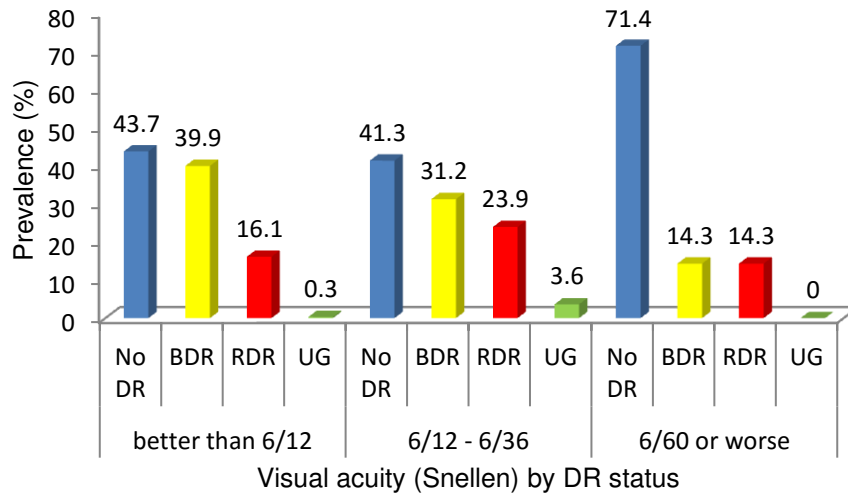
The majority (97.0%) of persons had a habitual visual acuity (with or without spectacles or with pinhole correction if habitual vision was worse than 6/9) of better than 6/12 (normal vision) in their better seeing eye at their first screening event (Figure 3.4.12). 2.8% had a visual acuity of 6/12 - 6/36 (visual impairment) and 0.1% had a visual acuity of 6/60 or worse (blind).

Figure 3.4.12: Visual acuity at first screening with the DRSSW in persons with T1DM



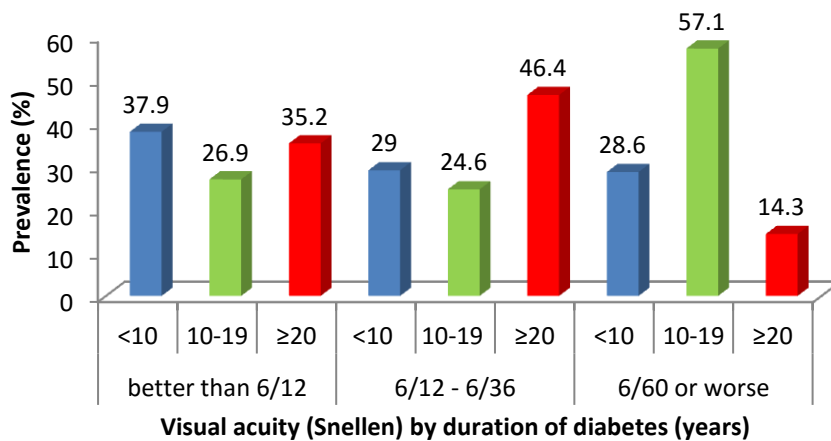
The prevalence of no DR, BDR and RDR was similar in those with normal vision and those with visual impairment (Figure 3.4.13). Surprisingly the prevalence of no DR increased from 43.7% in those with normal vision to 71.4% in persons who were categorised as blind and therefore the low VA in this group was due to causes other than DR. The prevalence of BDR and RDR decreased from 39.9% and 16.1%, respectively in those with normal vision to 14.3% (for both BDR and RDR) in persons who were blind. Therefore, the inference is that in the majority of persons who were categorised as blind the low VA was not caused primarily by DR. The number of ungradeable images increased in those with visual impairment 3.6% (compared to those with normal vision 0.3%) but surprisingly decreased in those classified as blind 0%. These results however, may be skewed by the small number of persons with visual impairment or blindness (n=145).

Figure 3.4.13: Visual acuity by the DR level



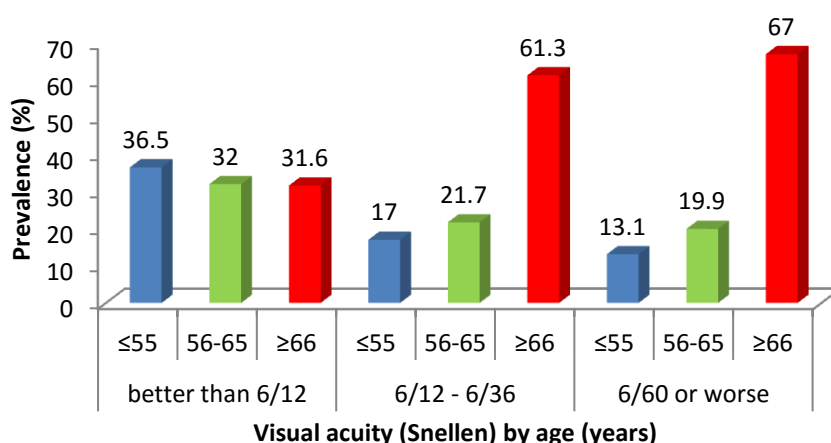
The prevalence of normal visual acuity was evenly distributed across the pre-defined categories of duration of diabetes (Figure 3.4.14). The prevalence of visual impairment was highest in those with a duration of ≥ 20 years (46.4%) and blindness was highest in those with diabetes for 10-19 years (57.1%).

Figure 3.4.14: Visual acuity by the duration of diabetes in persons with T1DM



There was an even distribution of age within the normal visual acuity category (Figure 3.4.15). The majority of visual impairment (61.3%) and blindness (67.0%) occurred in persons aged 66 yrs or older.

Figure 3.4.15: Prevalence of visual acuity by age in persons with T1DM



Any DR – any diabetic retinopathy; BDR – background diabetic retinopathy; RDR – referable diabetic retinopathy; UG - ungradeable

3.4.2.3 Summary of main findings

- Prevalence of visual impairment and blindness within the population undergoing screening was low at 6.6% and 0.4% respectively for persons with T2DM and 2.8% and 0.1% respectively for those with T1DM
- In persons with T2DM, the proportion with visual impairment and blindness increased as DR status worsened, with increasing numbers of ungradeable images
- Persons with T2DM aged ≥70 years and those with T1DM aged ≥66 years accounted for the majority of visual impairment and blindness.

- In persons with T1DM, the majority of those who were blind were for reasons other than DR. However there were very few T1DM who were blind and therefore results need to be interpreted with caution.

3.5 Discussion

Direct comparison of prevalence rates for DR between studies is inherently difficult due to the changing classification of diabetes with time, different image capture, technologies, professionals and grading protocols as well as the differences between the populations studied. The studies reporting prevalence rates for DR along with the different methodologies employed are summarised in Table 3.5.1 (page 96). (Klein et al. 1984a, b, Kristinsson et al. 1994b, Kristinsson et al. 1994a, Younis et al. 2002, Misra et al. 2009, Zhang et al. 2010, Yau et al. 2012)

In this community based study population the overall prevalence of any DR (T2DM and T1DM combined) was 32.4% which is similar to that reported for the US at 32.8%, (Zhang et al. 2010) and only slightly lower than 34.6% reported by a more recent global review based on studies involving retinal imaging. (Yau et al. 2012) In contrast, the overall prevalence of RDR in our study was 5.0%, of which 3.4% would be classed as sight-threatening DR which is lower than the 5.2% and 10.2% reported in the US (Zhang et al. 2010) and the global review respectively. (Yau et al. 2012) Both of these studies had differences in the ethnicity make up of their populations, with Zhang et al having an almost even distribution of non-Hispanic whites (26.4%), non-Hispanic blacks (38.8%) and Mexican Americans (34%) and Yau et al having a higher proportion of Caucasians (44.4%), and lower proportions of other ethnic groups Asians (30.9%), Hispanic (13.9%) and African American

(8.9%). Whilst the DRSSW did not have information available on the ethnicity of its population, the population of Wales is mainly Caucasian (95.6%).(Office for National Statistics 2012) Therefore, this difference in ethnicity of the different populations may offer an explanation for the lower prevalence of sight-threatening DR within the DRSSW especially as certain ethnic groups such as Asians and African populations have previously been shown to have an increased risk of sight-threatening DR when compared to Caucasians.(Ross et al. 2007, Stolk et al. 2008, Thomas et al. 2013) Distribution of risk factors may also contribute to these differences.

In our study involving persons with T2DM the prevalence of any DR was 30.3%, lower than that reported in the WESDR at 46.6%,(Klein et al. 1984b) as well as in Iceland at 41.0%.(Kristinsson et al. 1994b) In contrast some of the other UK screening programmes in Liverpool and Norwich, as well as the above mentioned global review, reported similar lower prevalence rates of DR in T2DM not dissimilar to ourselves at 25.3%, 25.3% and 25.2% respectively.(Younis et al. 2002, Misra et al. 2009, Yau et al. 2012)

In persons with T1DM in our study the prevalence of any DR at 56.0%, which was lower than previously reported in both the WESDR at 70.3%,(Klein et al. 1984a) and the more recent global review at 77.3%,(Yau et al. 2012) but similar to that seen in Iceland at 53.5%, (Kristinsson et al. 1994a) and only slightly higher than in the Liverpool screening programme at 45.7%.(Younis et al. 2002) The lower prevalence rates seen in this study compared to that reported in the WESDR study may be due to the reduction in prevalence of DR over time due to advances in diabetes care .(Vallance et al. 2008, Downie et al. 2011)

In our study the prevalence of RDR was 4.4% in persons with T2DM and 16.4% in persons with T1DM. This was considerably lower compared to the recent global review at 6.9% in T2DM and 38.5% in T1DM. (Yau et al. 2012) The Liverpool screening programme also reported a slightly higher prevalence of RDR in persons with T2DM at 6.0%, but a similar prevalence in persons with T1DM at 16.4%, (Younis et al. 2002) and Iceland at 16.9%. (Kristinsson et al. 1994b) In marked contrast the Norwich screening programme reported a very much lower prevalence of RDR in their T2DM population at 0.6%. (Misra et al. 2009) The difference between our findings and that reported by the Norwich screening programme is likely to be due differences in the definition of RDR in our study and sight-threatening DR in theirs. RDR includes PPDR or worse and/or exudative maculopathy whereas PPDR would be excluded from definition of sight-threatening DR and only treatable maculopathy included rather than all exudative maculopathies. (Misra et al. 2009)

Of the risk factors available, increasing duration of diabetes was the most significantly associated with the presence of any DR, BDR and RDR both in T2DM and T1DM. The odds ratios were much lower in T2DM compared to T1DM, however the stratification on the basis of duration of diabetes were different; for persons with T2DM the subgroups were <5, 5-9 and ≥ 10 years and for persons with T1DM the subgroups were <10, 10-19 and ≥ 20 years). The risk of all grades of DR increased with duration of diabetes being particularly high in those with diabetes duration of >10 years for T2DM and >20 years for T1DM. The duration of diabetes has been shown in almost all prevalence studies of DR to be the most important characteristic associated with an increased risk. (Klein et al. 2003)

In persons with T2DM the risk of all grades of DR, especially RDR, was considerably higher for those on insulin therapy. However, this could be an epiphenomenon with the need for insulin therapy reflecting a more advanced disease state, and not necessarily a direct cause of DR.(Thomas et al. 2014) However, other studies have directly linked the use of insulin therapy with increased risk of DR.(Zhao et al. 2014) In a meta-analysis of 7 cohort studies conducted in Europe (n=5), America (n=1) and China (n=1), between 1967 and 2010, including 19,107 persons with T2DM, insulin use was found to be associated with DR.(Zhao et al. 2014) When the analysis was adjusted for duration of diabetes, insulin use was no longer associated with DR. This demonstrates the inter-relationship between the different risk factors for DR for example, the younger age at diagnosis of diabetes, the longer the duration of diabetes and therefore, the greater chance of requiring insulin therapy. However, some studies have identified a transient worsening of DR at the initiation or intensification of insulin therapy.(The Diabetes Control and Complications Trial Research Group 1998, Henricsson et al. 2002) This may also be an indirect relationship via the improvement in glycaemic control, as rapid improvement has been shown to worsen DR with subsequent re-establishment of poor control apparently improving DR.(Dahl-Jorgensen et al. 1985, Chantelau et al. 2003)

There was a low level of visual impairment and blindness within the population undergoing screening in Wales, UK for both type of diabetes. The reason for the low prevalence of blindness within the DRSSW is likely due to the services exclusion criteria which excludes persons who were blind in both eyes. The reason for this exclusion from screening is due to difficulties they may have seeing and therefore following lights within the retinal cameras during photography or are under the care of HES. Therefore these persons are not referred to the DRSSW by their

GP. The prevalence of visual impairment and blindness were higher in persons with T2DM at 6.6% and 0.4% respectively compared to T1DM at 2.8% and 0.1% respectively. This difference may be a reflection of the age difference between the populations, with those persons with T2DM being older (mean 65 years) than those with T1DM (mean 37 years), rather than due to a difference in the type of diabetes. Other studies have reported overall levels of visual impairment and blindness of 2.9% and 0.5%,(Scanlon et al. 2008) 3.4% and 0.8%,(Broadbent et al. 1999) and 3.4% and 0.4%,(Sivaprasad et al. 2012) respectively in their target populations undergoing screening and 2.8% and 0.8%,(Prasad et al. 2001) in a clinic population of persons with diabetes. However, none of these studies reported visual acuity separately for type of diabetes.

There was an increase in the proportion of ungradeable images in persons with visual impairment and blindness in both T2DM and T1DM. Therefore visual impairment and blindness was probably related predominantly to other causes such as cataract or media opacities. Information on other eye conditions found during the screening process was not available for analysis in this study and therefore this could not be confirmed. The proportion of RDR in persons with T2DM increased from 4% in those with normal vision to 7.5% in those with visual impairment and 10% in those who were blind. In persons with T1DM RDR increased slightly in persons with visual impairment to 23.9% from 16.1% in persons with normal vision and then fell to 14.3% in persons who were blind. However the number of persons with T1DM who were blind were small and the majority had ungradeable images. This is to be expected as DR is still a major a cause of blindness.(Bunce et al. 2008)

There was also an increased risk of visual impairment and blindness associated with increased duration of diabetes in persons with T2DM. This agrees with a

recent survey of US adults aged 20 years or more where duration of ≥ 10 years was a significant risk factor for non-refractive visual impairment.(Ko et al. 2012) The majority of those persons considered visually impaired and blind were aged >70 years in persons with T2DM ($>70\%$) and ≥ 65 years in those with T1DM ($>60\%$). This finding was not unexpected as conditions such as damage to the cornea, cloudy or less pliable lens, damage to the retina and optic disc and other pathologies such as age related macular degeneration are more prevalent in an aging population.(Zacks 2006)

Limitations of this study were the exclusion of those persons with diabetes in Wales who were ineligible for screening (exclusions: under the age of 12 years, under the care of a HES and considered medically unfit for screening), non-compliance with screening and the exclusion of persons with incomplete or erroneous data (no recorded type of diabetes, type of diabetes or age at diagnosis of diabetes unrepresentative of the diagnosis). Therefore, the true prevalence of DR, and especially sight-threatening DR, in Wales could be higher than that reported here for the defined population especially due to the exclusion of those under the care of HES. Therefore we have investigated the prevalence of DR and especially sight-threatening DR in persons under the care of the hospital eye services in Wales who have not been screened by the DRSSW.(Richards 2014) This study has found that in 2012 there were 3,995 persons with diabetes under the care of HES in Wales that had not been screened by the DRSSW. To date the audit has looked at approximately 51.5% (2,058) of these persons (predominately located in the South) and has found that 32.4% have no DR, 9.1% have BDR and 44.5% have RDR, a further 14% had no mention of DR in their medical records. Adding these findings to the prevalence estimates in this chapter would give estimates of prevalence for Wales of 64.7% without DR, 26.9% with BDR and 6.2% RDR which is not very

dissimilar to the prevalence rates reported without the data from the HES. The availability of only limited putative risk factors is another limitation, which will be addressed in future studies.

Previous studies relating to the prevalence of DR have also had issues of ascertainment and non-compliance (Klein et al. 1984a, b, Kristinsson et al. 1994b, Kristinsson et al. 1994a, Younis et al. 2002, Misra et al. 2009, Zhang et al. 2010, Looker et al. 2012, Yau et al. 2012) and have incorporated inclusion criteria based on an age at diagnosis. In Wales approximately 20% of persons entitled and invited to screening do not attend appointments, and therefore no information is available on the characteristics or DR level within this population. However, the strengths of this study were its large population size (despite the exclusions), it is community based and involved systematic screening with standardised quality assured procedures and equipment for both photography and grading. Importantly both graders and photographers are quality controlled to ensure a consistency across all procedures involved in the acquisition and grading of the retinal images.

Our findings will provide policy makers additional information for planning future eye care services within our communities, with the proviso that the prevalence rate may be slightly underestimated as mentioned above. The prevalence of DR observed re-emphasises the need for continued systematic community based screening to prevent the loss of vision and blindness in this highly susceptible population. The detection of RDR at an early stage is essential to ensure timely onward referral for further assessment and possible treatment with improved outcome. Detection of BDR also provides an opportunity, where necessary, to improve glycaemic and blood pressure control and therefore help prevent the progression of DR. For the first time in 5 decades, DR is no longer the leading cause of blind certification in

England and Wales, inferring that with improved care for diabetes and early detection of DR through screening, the incidence of blindness due to diabetes can be reduced.(Liew et al. 2014)

3.5.1 Summary of main findings

- The Overall prevalence of any DR was 32.3% with 27.3% BDR and 5.0% RDR
- The prevalence of DR was lower in persons with T2DM (any DR 31.0%, BDR 26.6% and RDR 4.4%) compared to those with T1DM (any DR 56.2%, BDR 39.8% and RDR 16.4%)
- Duration of diabetes was the strongest risk factor for the prevalence of DR in both T2DM and T1DM after adjusting for confounders. However putative risk factors were limited in this dataset to age, gender, duration of diabetes and in T2DM treatment of diabetes.
- The prevalence of visual impairment and blindness in both T2DM and T1DM populations was low at 6.6% and 0.4% respectively and 2.8% and 0.1% respectively.
- These prevalence figures may slightly underestimate the true prevalence of DR and especially sight-threatening DR but also visual impairment and blindness due to the exclusion criteria for screening adopted by the DRSSW and consequently the data available for analysis.

Chapter 4

Incidence of diabetic retinopathy and re-defining screening intervals based on risk factor analysis in the Diabetic Retinopathy Screening Service for Wales (DRSSW)

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4.1 Introduction

The primary aim of the DRSSW is to reduce the incidence of blindness due to DR, through regular screening in order to implement early interventions such as laser therapy and/or VEGF inhibitors to prevent blindness. Secondly, the early detection of DR also allows preventative measures to be initiated in an attempt to delay the onset and progression to sight-threatening DR by ensuring good blood glucose and blood pressure control, and improving lipid levels if and when necessary.(Garvican et al. 2000, Harding et al. 2003) The screening interval for DR programmes in the UK was initially set at yearly intervals based on the opinion of experts and stated in the National Guidelines and to concur with the annual review requirement for all persons with diabetes.(Garvican et al. 2000, Department of Health 2001) The guidelines recognised that this initial screening interval would be reviewed after evidence was accumulated over a number of years. This is under consideration by the NSC at the present time.

Since systematic annual screening was introduced it has been suggested that annual screening is unnecessary for all persons with diabetes and that a stratified screening interval based on the level of risk would be more appropriate, safe and cost-effective.(Younis et al. 2003a, Younis et al. 2003b, Olafsdottir et al. 2007, Agardh et al. 2011, Aspelund et al. 2011, Chalk et al. 2012, Jones et al. 2012, Looker et al. 2013, Porta et al. 2013, Stratton et al. 2013) However, opinions on this have differed with some arguing that overly long intervals may lead to difficulties in maintaining contact with patients and may lead to complacency and non-compliance in certain patients.(Fong et al. 2001) Klein in 2003 stated that *'before adopting new guidelines for intervals for retinal examination in individuals with type 2 diabetes, effectiveness in achieving a significant reduction in vision loss from diabetes at least*

similar to that achieved by routine yearly dilated-eye examinations should be demonstrated.(Klein 2003)

For this purpose data from a large regional or national programme is required, which was not available and had not been reported prior to this study.(Thomas et al. 2012) Therefore, to date the National guidelines for screening for DR have not changed the recommendations for screening intervals in the UK, which remain at annual.(Garvican et al. 2000, UK National Screening Committee 2007, UK National Screening Committee 2009) However, currently there is an ongoing Four Nations diabetic retinopathy screening intervals project which is analysing data from seven UK screening programmes including the national programmes in Wales, Scotland and Northern Ireland and four of the 84 regional programmes in England.(Four Nations Study Group 2013) The study found that with the caveats that screening programmes have robust IT systems and quality assured grading that those persons with two consecutive negative annual screening events are at lowest risk of developing RDR and can therefore have subsequent screening intervals once every two-three years. The group reported their findings to the National screening Committee in November 2014 who will make recommendations regarding changing or maintaining the current screening interval.

4.2 Aims

The primary aim of this chapter was to determine the possibility of safely extending the screening interval for DR in persons with diabetes without evidence of DR at initial screening as determined using 2 x 45 degree fields per eye following mydriasis (see Chapter 2). In order to assess the question of screening intervals the following aims were investigated:

- The cumulative incidence of any DR, BDR and RDR in persons with T2DM and T1DM over a four year period (2005-2009) and,
- the risk factors associated with the incidence of any DR, BDR and RDR in both T2DM and T1DM over the study period (2005-2009).

4.3 Methods

All persons attending the DRSSW between 2005 and 2009 without evidence of DR at their first screening event who underwent at least one additional screening event, were included in the analysis.

Details of the statistical methods used in this study are fully described in Chapter 2.

In addition to the basic descriptive analyses used throughout, survival analyses; Kaplan Meier and Cox proportional hazards methods were also used in order to estimate the incidence of any DR, BDR and RDR as well as examine the impact of the limited number of putative risk factors, known to be associated with the development of DR, that were available for analysis. The log rank test was used to assess differences between the Kaplan Meier curves with $p < 0.05$ taken as significant. Cox regression is presented as hazard ratios (HR) with 95% CI.

Thereafter, incidence rates of RDR were calculated, in order to examine the effect stratifying screening intervals by the identified risk factors would have within this population. For T2DM the stratification was based on treatment of diabetes divided as; diet alone, OHA or insulin and known duration of diabetes i.e. < 5 years, 5-9 years and ≥ 10 years. For T1DM the stratification was based on duration of diabetes alone divided as ≤ 10 years, 11-19 years and ≥ 20 years. The incidence of RDR was calculated for these groups to determine how many cases of RDR would be at risk of a delay in diagnosis of RDR if the screening interval were to be extended beyond one year, the current screening interval.

4.4 Results

Of the 60,566 persons with diabetes without evidence of DR at initial screening 85.1% (51,556) had at least 1 further screening event within the study period and were therefore included in the following analysis. Among the reasons for not having a second screening event included: time between first screening and end of study being <12 months, cancellation of appointments, non-attendance due to death, ill-health, unknown reasons and also when the patient changed their GP to one outside Wales. Due to the anonymisation process this aspect could not be investigated further.

4.4.1 T2DM

4.4.1.1 Incidence of DR over a period of 4 years

Of the 57,199 persons with T2DM without evidence of DR at the first screening event, 87.0% (49,763) had at least a second screening event within the 4 year study period. 13.0% (7,436) did not attend for further screening during the study period, 6.0% (449) of whom were not eligible for a second screen, as this would have been within 12 months (first screen in 2009). The remainder 94.0% (6,987) did not undergo repeat screening for unknown reasons.

The demographic characteristics of those who did not have a second screening event despite being eligible compared with those included in the analysis are included in Table 4.4.1. Those excluded from the analysis were significantly older by two years both at time of screening and at diagnosis of diabetes when compared to those retained in the study.

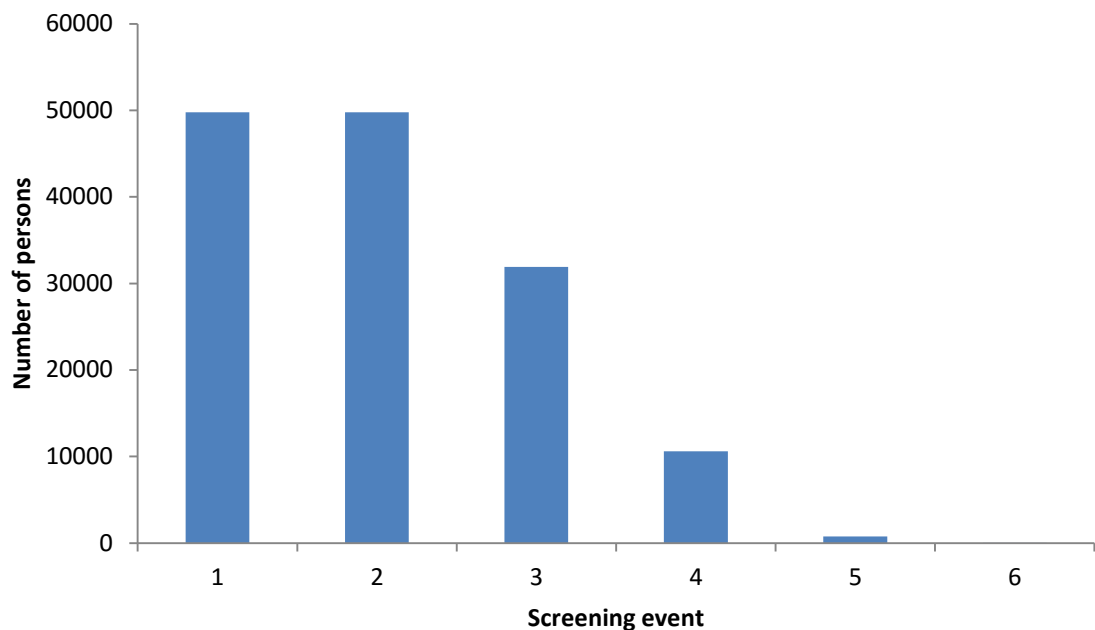
Table 4.4.1: Characteristics of those persons with T2DM who did or did not attend more than 1 screening event.

Characteristics	No repeat screening event (eligible)	At least 1 further screening event	P value
n	6,987	49,763	
Age years mean (SD)	66.9 (13.5)	64.4 (11.3)	<0.001
Known duration of DM years median (IQR)	3.0 (1.0-6.0)	3.0 (1.0-6.0)	0.026
Age when DM diagnosed years mean (SD)	62.3 (13.2)	60.2 (11.3)	<0.001
Gender: n (%)			0.087
Male	3,794 (54.3)	27,529 (55.3)	
Female	3,175 (45.4)	21,975 (44.2)	
Unknown	18 (0.3)	259 (0.5)	
Treatment for DM: n (%)			<0.001
Diet	2,684 (38.4)	17,236 (34.6)	
OHA	3,787(54.2)	29,049 (58.4)	
Insulin	394 (5.6)	2,669 (5.4)	
Unknown	122 (1.7)	809 (1.6)	

n – total numbers; SD – standard deviation; IQR – interquartile range; OHA – oral hyperglycaemic agents; n - number

Of the 49,763 persons with at least two screening events 31,924 (64.2%) had a third, 10,615 (21.3%) a fourth, 767 (1.5%) a fifth and 3 (0.006) a sixth screening event during the four year study period (Figure 4.4.1). Reasons for having more than four screening events within the four year study period would be technical failures with a 3 month recall or a re-referral from GP or optician. The median (IQR) interval between the first and second screening event was 16 (13-20) months, second and third screening was 14 (12-17) months, third and fourth was 13 (12-14) months, fourth and fifth was 12 (11-13) months, and fifth and sixth was 12 (11-13) months. Due to the high dropout rate the findings beyond the third screening event should be interpreted with caution.

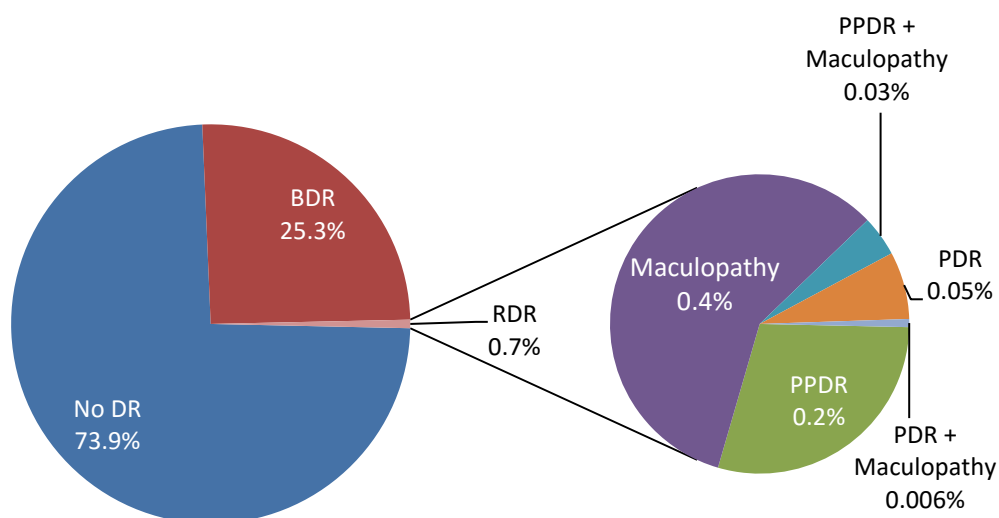
Figure 4.4.1: Number of persons with T2DM at each screening event



At their final screening event 73.9% remained without evidence of DR (Figure 4.4.2) and 26% (12,922) developed DR, which consisted of 25.3% (12,574) BDR and 0.7% (348) RDR. RDR comprised of 0.2% (107) PPDR, 0.4% (197) maculopathy, 0.03% (16) PPDR plus maculopathy, 0.05% (25) PDR, and 0.006% (3) PDR with maculopathy. In those who developed PDR (28), the duration of diabetes was less than 5 years in 19 persons (68%), 27 persons (96%) were on diet and oral therapy and only one subject was receiving insulin therapy. 67.9% (19) of PDR were detected at the second screening event with a mean screening interval of 1.7 (± 0.8) years. Those who developed PDR at their second screening event were older than the mean age of the total population at 69.4 (± 9.0) years vs. 64.4 (± 11.3), older at diagnosis of diabetes 65.5 (± 9.5) years vs. 60.2 (± 11.3) years and more were male 68.4% vs. 55.3%. However, the duration of diabetes (median 3.0 years, IQR 0.5) and proportions on insulin therapy (5.3%) were similar compared to the total population. As the putative risk factors of known duration of diabetes and use of insulin therapy are not indicated in this small subset of patients, other risk factors

not available for analysis here such as poor glycaemic control, may be contributing to this rapid progression to PDR.

Figure 4.4.2: Incidence of any DR, BDR and RDR over the four year study period in persons with T2DM



No DR - no diabetic retinopathy; BDR - background diabetic retinopathy; RDR - referable diabetic retinopathy; PPDR - preproliferative diabetic retinopathy; PDR - proliferative diabetic retinopathy

The estimated annual and cumulative incidence (cases per 1,000 persons) of any DR, BDR and RDR are included in Table 4.4.2. The annual incidence of DR was low at 8 cases for both any DR and BDR and no cases of RDR. Between 2 and 4 years following a negative screening event the annual incidence of DR increased at a relatively constant rate with an average of 145.7 cases of any DR, 143.3 cases of BDR and 8.7 cases of RDR (Figure 4.4.3a). The four year cumulative incidence of any DR, BDR and RDR was 445, 438 and 16 cases respectively (Figure 4.4.3b).

Table 4.4.2: Incidence of any DR, BDR and RDR during the four year study period in persons with T2DM

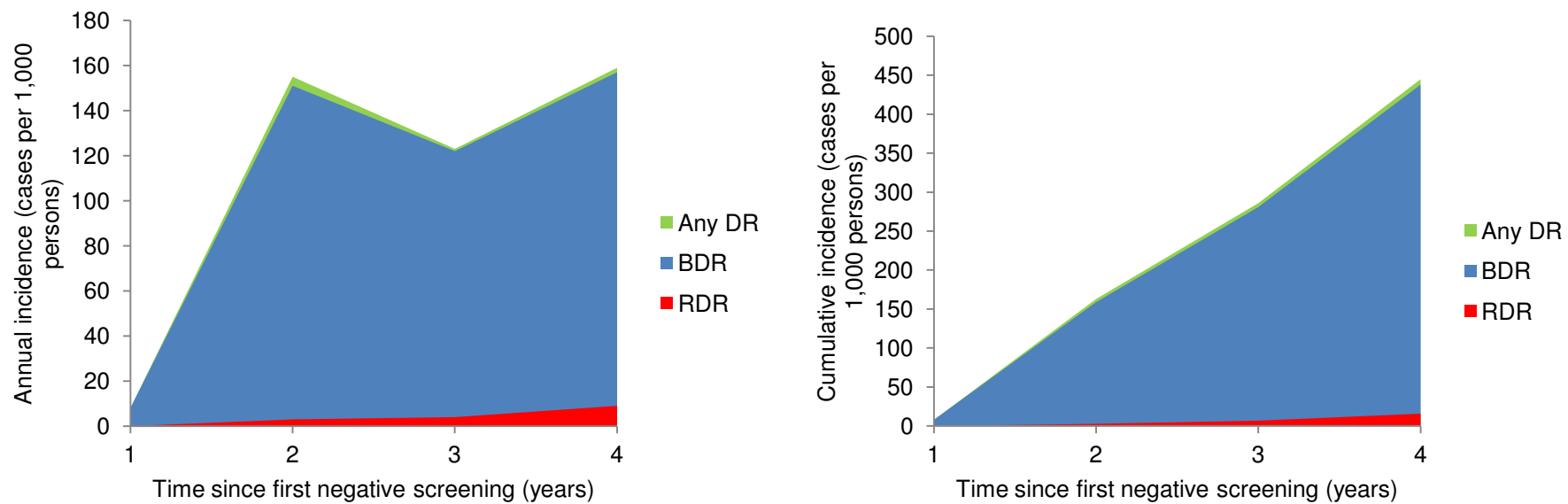
Time (years)	Any DR		
	n	Annual Incidence	Cum Incidence (95% CI)
1	48,793	8.00	8.00 (7.9997-8.0003)*
2	30,693	155.00	163.00 (162.99-163.01)
3	16,110	123.00	286.00 (285.98-286.02)
4	3,107	159.00	445.00 (444.84-445.16)

Time (years)	BDR		
	n	Annual Incidence	Cum Incidence (95% CI)
1	48,457	8.00	8.00 (7.9997-8.0003)*
2	30,573	151.00	159.00 (158.99-159.01)
3	15,026	122.00	281.00 (280.97-281.03)
4	3,098	157.00	438.00 (437.84-438.16)

Time (years)	RDR		
	n	Annual Incidence	Cum Incidence (95% CI)
1	49,083	0.00	0
2	35,436	3.00	3.00 (2.9998-3.0002)
3	19,274	4.00	7.00 (6.9993-7.0007)
4	4,351	9.00	16.00 (15.993-16.007)

Incidence and cumulative incidence is per 1,000 persons, Any DR - any diabetic retinopathy; BDR - background diabetic retinopathy; RDR - referable diabetic retinopathy; n - number remaining at risk; 95% CI – 95% Confidence Interval; * more than 2 decimal places provided due to the very narrow confidence intervals;

Figure 4.4.3: a) Annual and b) cumulative incidence of Any DR, BDR and RDR in persons with T2DM.
a) b)



Ann. inc. - annual incidence; Cum. inc. - Cumulative incidence; any DR - any diabetic retinopathy; BDR - background diabetic retinopathy; RDR - referable diabetic retinopathy

4.4.1.2 Risk Factors for incident DR

The baseline characteristics of the persons with T2DM are summarised in Table 4.4.3 divided into four groups according to outcome, i.e. those who did not develop DR and those who developed either any DR, BDR or RDR. Those who remained free of DR were slightly but significantly younger at first screening than those who developed any DR and BDR but older than those who developed RDR.

Table 4.4.3: Characteristics of persons with T2DM who developed DR and those who remained free of DR in persons with T2DM

	Remain No DR (n = 36,841) Reference category	Develop any DR (n = 12,922)	P value No DR vs. any DR	Develop BDR (n = 12,574)	P value No DR vs. BDR	Develop RDR (n = 348)	P value No DR vs. RDR
Age mean (SD)	64.2 (11.3)	64.9 (11.3)	0.002	65.0 (11.3)	<0.001	62.9 (11.3)	0.005
Known Duration of DM median (IQR)	3.0 (1.0-5.0)	4.0 (2.0-7.0)	<0.001	4.0 (2.0-7.0)	<0.001	4.0 (2.0-7.0)	<0.001
Age at diagnosis mean (SD)	60.3 (11.3)	59.8 (11.5)	<0.001	59.8 (11.5)	<0.001	57.3 (11.8)	<0.001
Gender:			0.232		0.403		0.786
Male n (%)	20,346 (55.5)	7,183 (55.9)		6,988 (55.9)		195 (56.2)	
Female n (%)	16,316 (44.5)	5,659 (44.1)		5,507 (44.1)		152 (43.8)	
Treatment of DM:			<0.001		<0.001		<0.001
Diet n (%)	13,918 (38.5)	3,318 (26.0)		3,246 (26.2)		72 (20.7)	
OHA n (%)	20,723 (57.3)	8,326 (64.4)		8,092 (65.2)		234 (67.2)	
Insulin n (%)	1,555 (4.3)	1,114 (8.6)		1, 072 (8.6)		42 (12.1)	

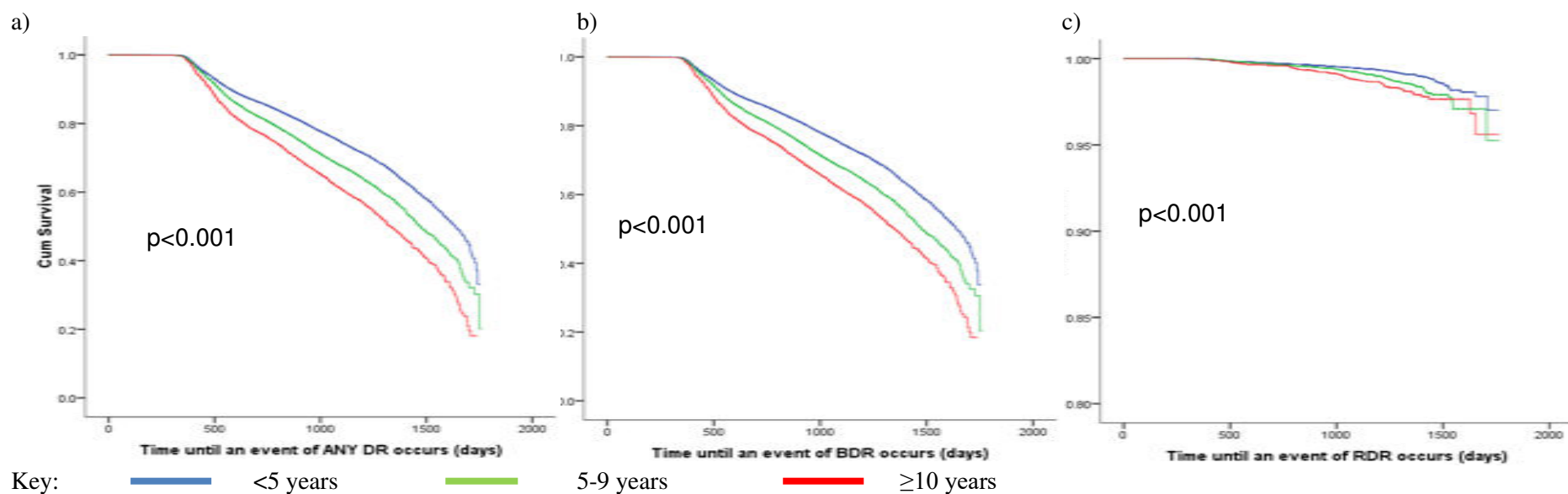
No DR - no diabetic retinopathy; any DR - any diabetic retinopathy; BDR - background diabetic retinopathy; RDR - referable diabetic retinopathy; SD - standard deviation; IQR - interquartile range; OHA - oral hyperglycaemic agents

Known duration of T2DM

Those who did not develop DR during the 4 year study period had a significantly shorter known duration of diabetes (3 years), compared to those who developed any DR (4 years), BDR (4 years) or RDR (4 years) (Table 4.4.3, page 149).

Significant differences were seen in the survival curves for known duration of diabetes and the incidence of any DR, BDR and RDR over the study period (Figure 4.4.4a-c). Those with diabetes for ≥ 10 years had a greater likelihood of developing any DR, BDR and RDR compared to those with diabetes for < 5 years, with differences between the survival curves evident from approximately 1.4 years onwards for the presence of any DR and BDR and 2.2 years for RDR. After adjusting for age at diagnosis of diabetes, gender and treatment of diabetes, increasing known duration of diabetes increased the risk of any DR, BDR and RDR developing (Table 4.4.4, page 152). Those with a known duration of diabetes of ≥ 10 years had a 1.6-fold increased risk of developing any DR and BDR and a 1.5-fold increased risk of developing RDR relative to those persons with a known duration of diabetes of < 5 years.

Figure 4.4.4: Kaplan Meier survival curves for the development of DR and known duration of diabetes in persons with T2DM



		<5 years				5-9 years				≥ 10 years			
		1 year	2 years	3 years	4 years	1 year	2 years	3 years	4 years	1 year	2 years	3 years	4 years
Any DR	Number of people remaining at risk	31,901	19,968	9,698	1,951	11,732	7,589	3,784	789	5,160	3,136	1,592	367
	Number of cases	226	3,951	5,926	7,048	102	1,983	2,994	3,567	68	1,096	1,625	1,931
BDR	Number of people remaining at risk	31,725	19,908	9,674	1,945	11,630	7,553	3,768	787	5,102	3,112	1,584	366
	Number of cases	222	3,831	5,770	6,874	97	1,912	2,903	3,462	65	1,059	1,572	1,871
RDR	Number of people remaining at risk	32,064	22,572	11,961	2,645	11,812	8,963	5,041	1,121	5,207	3,901	2,272	585
	Number of cases	4	79	124	166	3	35	64	101	1	19	43	59

Table 4.4.4: Cox regression analysis for the development of any DR, BDR and RDR in persons with T2DM

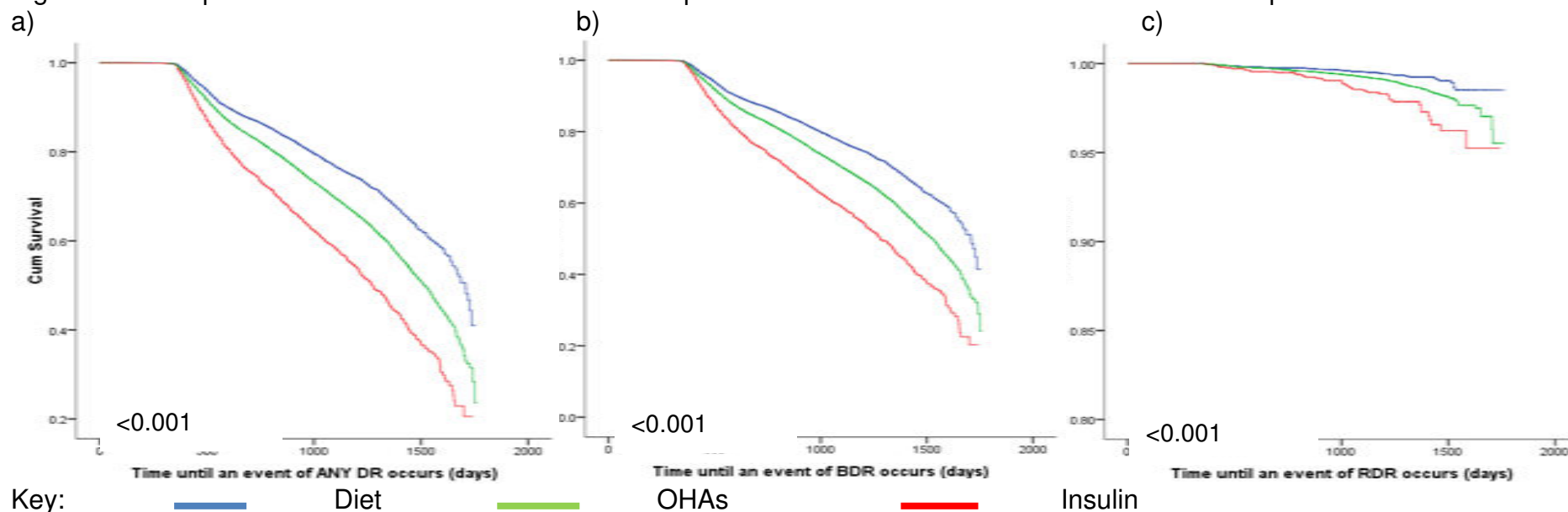
	Any DR (12,922)		BDR (12,574)		RDR (348)	
	Crude hazard Ratio (95% CI)	Adjusted hazard Ratio (95% CI)	Crude hazard Ratio (95% CI)	Adjusted hazard Ratio (95% CI)	Crude hazard Ratio (95% CI)	Adjusted hazard Ratio (95% CI)
Age at diagnosis (years)						
30-49 (8,932)	1.00	1.00	1.00	1.00	1.00	1.00
50-59 (14,430)	0.94 (0.89, 0.94)	0.97 (0.92, 1.02)	0.94 (0.90, 0.99)	0.98 (0.93, 1.03)	0.71 (0.54, 0.94)	0.75 (0.56, 0.98)
60-69 (15,572)	0.92 (0.87, 0.96)	1.00 (0.95, 1.06)	0.93 (0.88, 0.98)	1.02 (0.96, 1.03)	0.50 (0.37, 0.68)	0.57 (0.42, 0.77)
≥70 (10,829)	1.03 (0.98, 1.09)	1.25 (1.18, 1.32)	1.04 (0.99, 1.10)	1.26 (1.19, 1.33)	0.70 (0.51, 0.95)	0.89 (0.64, 1.23)
Gender: Male (27,529)	1.02 (0.99, 1.06)	1.02 (0.99, 1.06)	1.02 (0.99, 1.06)	1.02 (0.99, 1.06)	1.03 (0.83, 1.27)	1.03 (0.83, 1.27)
Known Duration of DM (years)						
< 5 (32,574)	1.00	1.00	1.00	1.00	1.00	1.00
5-9 (11,922)	1.32 (1.27, 1.38)	1.25 (1.20, 1.30)	1.33 (1.27, 1.38)	1.25 (1.19, 1.30)	1.47 (1.16, 1.87)	1.31 (1.02, 1.67)
≥10 (5,297)	1.69 (1.61, 1.78)	1.59 (1.51, 1.68)	1.69 (1.60, 1.77)	1.59 (1.51, 1.68)	1.84 (1.38, 2.47)	1.52 (1.12, 2.06)
Treatment for diabetes:						
Diet (17,236)	1.00	1.00	1.00	1.00	1.00	1.00
OHA (29,049)	1.39 (1.34, 1.45)	1.34 (1.29, 1.40)	1.39 (1.34, 1.45)	1.34 (1.28, 1.40)	1.66 (1.27, 2.16)	1.52 (1.16, 2.00)
Insulin (2,669)	2.09 (1.96, 2.24)	1.87 (1.74, 2.01)	2.09 (1.95, 2.24)	1.86 (1.73, 2.00)	3.06 (2.09, 4.47)	2.44 (1.63, 3.65)

Any DR - any diabetic retinopathy; BDR - background diabetic retinopathy; RDR - referable diabetic retinopathy; 95% CI - 95% confidence interval; DM - diabetes mellitus; OHA - oral hyperglycaemic agent

Treatment of diabetes

There were significantly more persons who were on diet treatment and less using OHAs and on insulin therapy in those who remained free from DR compared to those who developed any DR, BDR and RDR (Table 4.4.3, page 149). There were also significant differences in the survival curves for the incidence of any DR, BDR and RDR and the three categories of treatment of diabetes (Figure 4.4.5). Those who were on insulin therapy had a poorer prognosis for the development of any DR, BDR and RDR. After adjusting for age at diagnosis of diabetes, duration of diabetes and gender those persons using insulin therapy were at a 1.9-fold increased risk of developing any DR or BDR and a 2.4-fold increased risk of developing RDR relative to those receiving diet (Table 4.4.4, page 152).

Figure 4.4.5: Kaplan Meier survival curves for the development of DR and known treatment of diabetes in persons with T2DM



		Diet				OHA				Insulin			
		1 year	2 years	3 years	4 years	1 year	2 years	3 years	4 years	1 year	2 years	3 years	4 years
Any DR	Number of people remaining at risk	16,907	10,342	4,867	982	28,527	18,424	9,316	1,935	2,599	1,597	840	181
	Number of cases	103	1,887	2,776	3,237	244	4,407	6,715	8,065	35	616	901	1,082
BDR	Number of people remaining at risk	16,837	10,315	4,854	980	28,302	18,346	9,287	1,929	2,558	1,582	890	180
	Number of cases	101	1,842	2,717	3,167	235	4,251	6,510	7,837	34	589	850	1,041
RDR	Number of people remaining at risk	16,978	11,499	5,795	1,256	28,723	21,537	12,202	2,794	2,618	2,026	1,247	289
	Number of cases	2	36	53	68	6	85	151	218	0	12	27	40

4.4.1.3 Screening Intervals

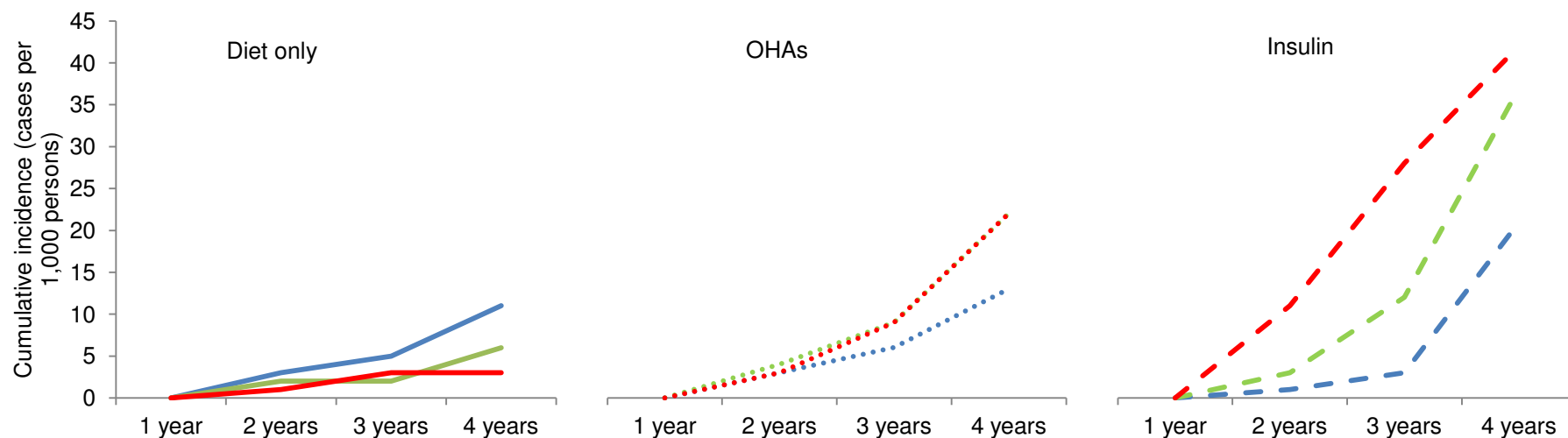
As known duration and type of treatment of diabetes were shown to be the most important putative risk factors for DR they were used to assess the cumulative incidence of RDR (cases per 1,000 persons) in order to examine the impact of varying the screening intervals (Figure 4.4.6).

There were no cases of RDR within the first year following an initial negative screening event for any of the groups according to treatment and/or duration of diabetes. Those persons treated by diet alone, with a known duration of diabetes of <5 years, had two and three year cumulative incidence of 3 and 5 cases respectively, compared to 3 and 6 cases for those using OHAs and 3 and 21 cases for those using insulin within the same duration group. In those with a known duration of diabetes was 5-9 years the two and three year cumulative incidence of RDR was 2 cases at two years and no additional cases at three years for those diet treated, 4 and 9 cases for those on OHAs respectively and 3 and 12 cases for those on insulin therapy respectively. If the known duration of diabetes was ≥ 10 years the 2 and 3 year cumulative incidence of RDR was 1 and 3 cases respectively for those on diet alone, 3 and 9 cases for those using OHAs and 11 and 28 cases for those using insulin (a 9 times higher rate compared to those diet controlled).

Screening intervals for persons with T2DM with a preceding negative screen could be increased to once every two years from annual, without putting anyone at an increased risk of a delayed diagnosis of RDR. In those persons treating their diabetes through diet alone, if the screening interval was once every three years then 6 cases would be at risk of a delayed diagnosis of RDR. In those persons treating their diabetes with OHAs a screening interval of once every three years would mean 10 cases were at risk of a delayed diagnosis of RDR, this could be

reduced to 7 cases if those who also had diabetes for ≥ 10 years remained on biennial screening. In those persons on insulin therapy 15 cases would be at risk of a delayed diagnosis with screening once every three years. However, if those with diabetes ≥ 10 years and using insulin remained on a biennial screening interval then the risk would reduce to 4 cases.

Figure 4.4.6: Cumulative incidence of RDR by known duration of diabetes and treatment of diabetes in persons with T2DM



Category	Total n	RDR Cases	Incidence of RDR*			
			1†	2†	3†	4†
< 5 yrs + Diet	13943	64	0	3	5	11
5-9 yrs + Diet	2429	6	0	2	2	6
≥ 10 yrs + Diet	864	2	0	1	3	3

Category	Total n	RDR Cases	Incidence of RDR*			
			1†	2†	3†	4†
< 5 yrs + OHA	17292	109	0	3	6	13
5-9 yrs + OHA	8240	85	0	4	9	22
≥ 10 yrs + OHA	3517	40	0	3	9	22

Category	Total n	RDR Cases	Incidence of RDR*			
			1†	2†	3†	4†
<5 yrs + Insulin	787	7	0	1	3	21
5-9 yrs Insulin	1072	16	0	3	12	37
≥ 10 yrs + Insulin	810	19	0	11	28	42

* incidence is cases per 1,000 persons; † number of years since first negative screening event

4.4.1.4 Summary of main findings

- In a population of 49,763 persons with T2DM, without evidence of DR at the first screening event, 348 (0.7%) persons developed RDR over the four year study period of which 28 (0.06%) developed PDR (\pm maculopathy).
- The four year cumulative incidence of any DR, BDR and RDR was 445, 438 and 16 cases per 1,000 persons respectively.
- Of the limited putative risk factors for DR available, known duration of diabetes and treatment modality were the most significant risk factors associated with the incidence of any DR, BDR and RDR after adjusting for age at diagnosis and gender.
- If the screening interval was extended from annual to biennial then no one (one year incidence of RDR 0 cases per 1,000 persons) would be at an increased risk of a delay in diagnosis of RDR.
- When the screening interval was stratified for persons with T2DM according to both duration of diabetes and treatment type it demonstrated that in addition to biennial screening:
 - Those persons on diet treatment only and those using OHA's with a duration of diabetes of <10 years could have a triennial screening interval with only 6 cases (for diet) and 7 cases (for OHAs) at risk of a delayed diagnosis of RDR.

4.4.2 T1DM

4.4.2.1 Incidence of DR over the four year study period

Of the 2,177 persons with T1DM who did not have DR at first presentation 82.4% (1,796) had at least one further screening event within the defined study period. Of those who did not have a repeat screening event (17.5%), 3.8% (14) were anyway

not eligible within the study period as the interval from the first screen this would have been <12 months. The reasons the remaining 96.3% (367) who were eligible for a repeat screening event within the study but did not receive one could not be investigated further due to the anonymised nature of the data. The baseline characteristics between those eligible but who did not receive any further screening within the study period and those who did are included in Table 4.4.5.

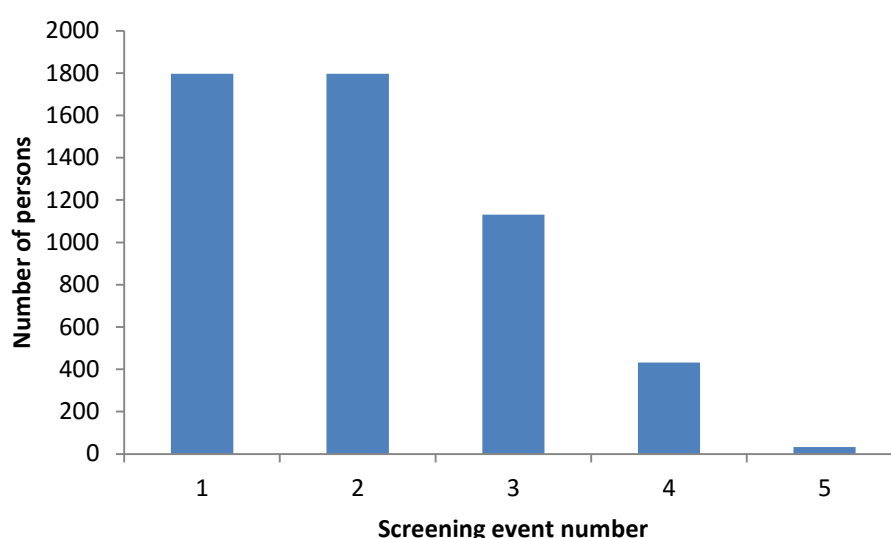
Table 4.4.5: Characteristics of those persons with T1DM who did or did not attend more than 1 screening event.

	Without a second screening event (n=367)	With more than one screening event (n=1,796)	P value
Age years mean (SD)	37.1 (21.3)	34.1 (18.7)	0.014
Gender n (%):			0.716
Male	203 (55.3)	971 (54.1)	
Female	164 (44.7)	818 (45.5)	
Unknown	0	7 (0.4)	
Duration of diabetes years median (IQR)	6.0 (3.0-12.0)	6.0 (3.0-12.0)	0.649
Age at diagnosis of diabetes years means (SD)	27.4 (19.5)	24.8 (16.7)	0.017

n – total number; SD – standard deviation; IQR - interquartile range;

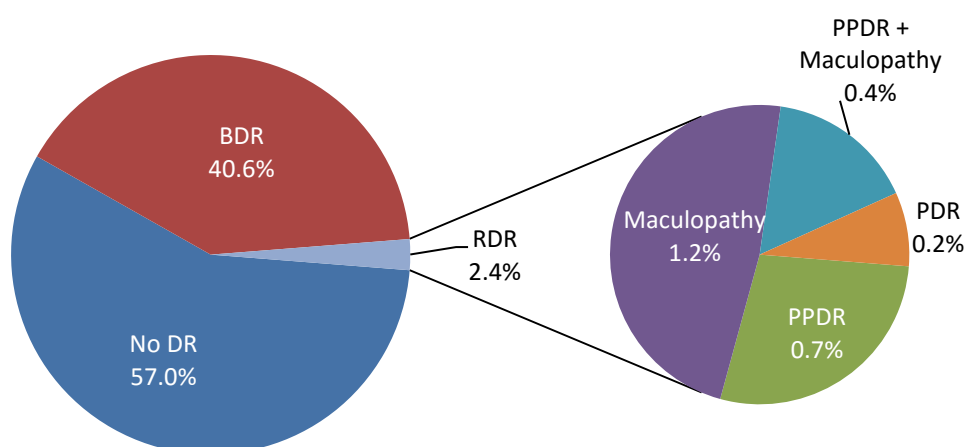
During the study a total of 1,131 (63.0%) persons had a third screening event, 432 (24.1%) a fourth and 32 (1.8%) a fifth screening event (Figure 4.4.7). The time between the first and second screening event 16 months (14-21), second and third 14 months (12-17), third to fourth 12 months (12-12) and fourth and fifth was 11.5 months (11-12). Due to the high dropout rate and small sample size findings beyond the third screening event should be interpreted with caution.

Figure 4.4.7: Number of persons with T1DM at each screening event



Of the 1,796 patients with T1DM without evidence of DR at first screening, 57.0% (1,023) remained free of DR at the end of the study (Figure 4.4.8). 43.0% (773) developed DR, comprising 40.6% (729) with BDR and 2.4% (44) RDR. The RDR group included 27.3% (12) with PPDR, 6.8% (3) PDR, 50.0% (22) maculopathy and 15.9% (7) PPDR with maculopathy. Of those who developed RDR, 56.8% (25) had BDR detected at an earlier screening event prior to the development of RDR. The three persons who developed PDR did so by their second screening event which was one, two and three years following their initial screening. Those few who developed PDR were relatively young at diagnosis of diabetes as compared to the whole group with a mean age (SD) of 16.3 (9.3) years and a longer duration of diabetes median (IQ) 7.0 (5.0-8.0) years at the time of first screening.

Figure 4.4.8: Incident DR over four years in persons with T1DM



No DR - no diabetic retinopathy; BDR - background diabetic retinopathy; RDR - referable diabetic retinopathy; PPDR - preproliferative diabetic retinopathy; PDR - proliferative diabetic retinopathy; RDR - referable diabetic retinopathy

The annual incidence (cases per 1000 persons) of any DR increased from 17 cases in the first year to 204 cases in the fourth year the majority of which were BDR (15 to 204 cases). The annual incidence of RDR increased from 1 case in the first year to 34 cases in the fourth year. The four year cumulative incidence of any DR, BDR and RDR was 649, 635 and 56 cases respectively (Table 4.4.6)

Table 4.4.6: Incident DR during the four year study in persons with T1DM

Any DR				
Time (years)	n	Annual incidence	Cum Incidence	95% CI
1	1,746	17.00	17.00	16.98, 17.02
2	1,014	247.00	264.00	263.62, 264.38
3	500	181.00	445.00	444.03, 445.97
4	105	204.00	649.00	644.75, 653.25

BDR				
Time (years)	n	Annual incidence	Cum Incidence	95% CI
1	1,707	15.00	15.00	17.98, 15.01
2	1,000	237.00	252.00	251.63, 252.37
3	495	179.00	431.00	430.03, 431.97
4	105	204.00	635.00	630.67, 639.33

RDR				
Time (years)	n	Annual incidence	Cum Incidence	95% CI
1	1,747	1.00	1.00	0.999, 1.001
2	1,023	8.00	9.00	8.98, 9.01
3	509	13.00	22.00	21.92, 22.08
4	107	34.00	56.00	55.03, 56.97

Any DR – any diabetic retinopathy; BDR – background diabetic retinopathy; RDR – referable diabetic retinopathy; Time - time since first negative screen; n - number remaining at risk; Cum incidence – cumulative incidence; 95% CI – 95% confidence interval;

4.4.2.2 Risk Factors for incident DR

Those who did not develop DR were significantly younger at initial screening aged 32.6 years compared to those who subsequently developed any DR and BDR, both 36.2 years of age (Table 4.4.7). Although those who developed RDR were older than those who remained without DR the difference did not reach significance. This finding may be an anomaly due to the small number of persons who developed RDR. Those who developed any DR, BDR and RDR were significantly older at diagnosis of diabetes compared to those who remained without DR throughout the study period.

Table 4.4.7: Differences in characteristics between those persons with T1DM who develop any DR, BDR and RDR and those who remain free of DR

	Remain No DR (n=1,023)	Develop Any DR (n=773)	P value No DR Vs any DR	Develop BDR (n=729)	P value No DR Vs BDR	Develop RDR (n=44)	P value No DR Vs RDR
Age years mean (SD)	32.6 (18.6)	36.2 (18.7)	<0.001	36.2 (18.7)	<0.001	36.7 (17.6)	0.148
Gender n (%):			0.011		0.039		0.003
Male	580 (56.7)	391 (50.6)		376 (51.6)		15 (34.1)	
Female	440 (43.0)	378 (48.9)		349 (47.9)		29 (65.9)	
Unknown	3 (0.3)	4 (0.5)		4 (0.3)			
Duration of DM years median (IQR)	4.0 (2.0-9.0)	8.0 (5.0-15.0)	<0.001	8.0 (5.0-15.0)	<0.001	6.0 (2.0-11.0)	<0.001
Age at diagnosis of DM years mean (SD)	25.4 (16.8)	24.1 (16.6)	0.125	24.4 (16.8)	0.260	19.1 (11.4)	0.001

No DR – no diabetic retinopathy; Any DR – any diabetic retinopathy; BDR – background diabetic retinopathy; RDR – referable diabetic retinopathy; n – total number; SD – standard deviation; IQR – Interquartile range;

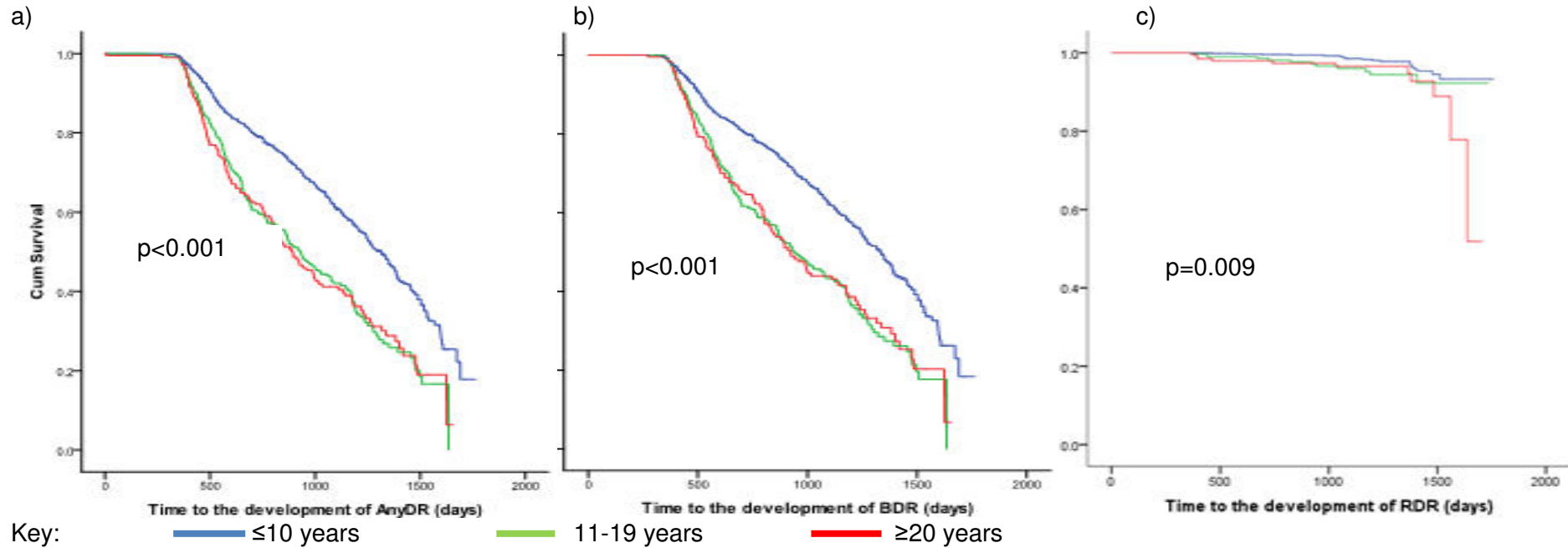
Duration of diabetes

There was a significant difference in the duration of diabetes at initial screening between those who remained free of DR and those who developed DR. Those who remained free of DR had a shorter duration of diabetes of 4 years compared to those developing DR i.e. any DR and BDR 8 years and RDR 6 years (Table 4.4.7, page 164).

Significant differences were evident in the survival curves for duration of diabetes and the incidence of any DR, BDR and RDR over the study period (Figure 4.4.9a-c). Those with a duration of diabetes of 11-19 years had similar survival curves to those with diabetes for ≥ 20 years, both representing a poorer prognosis for the development of any DR and BDR than those with diabetes for ≤ 10 years. There was a clear separation in the survival curve for those with a duration of diabetes of ≤ 10 years and those with a duration of diabetes > 10 years after 1.2 years for those who developed any DR and BDR. The survival curves for the incidence of RDR although statistically different appeared very similar over the main period of the study. However, the number of people developing RDR were small and so should be interpreted with caution.

After adjusting for age at diagnosis of diabetes and gender, increasing duration of diabetes remained the strongest risk factor which was associated with the incidence of any DR, BDR and RDR (Table 4.4.8, page 167). Those with diabetes for > 10 years were at an increased risk compared to those with diabetes for ≤ 10 years with those with diabetes for 11-19 years had a 1.8-fold increased risk for the incidence of any DR and BDR and a 2.2-fold increased risk of RDR, those with diabetes for ≥ 20 years had a 2.8-fold increased risk for the incidence of any DR, 1.8- for BDR and a 2.4- for RDR.

Figure 4.4.9: Kaplan Meier survival curves for the time to the incidence of DR for the duration of diabetes



		≤10 years				11-19 years				≥20 years			
		1 year	2 years	3 years	4 years	1 year	2 years	3 years	4 years	1 year	2 years	3 years	4 years
Any DR	Number of people remaining at risk	1,258	755	371	76	290	151	72	17	198	108	57	12
	Number of cases	20	234	368	450	6	112	150	174	5	72	105	121
BDR	Number of people remaining at risk	1,238	746	350	76	280	148	70	17	189	106	57	12
	Number of cases	19	222	368	429	4	103	140	162	3	63	94	110
RDR	Number of people remaining at risk	1,271	909	508	121	298	227	141	30	202	164	119	28
	Number of cases	1	5	11	19	0	5	9	12	0	4	6	8

Table 4.4.8: Cox regression survival analysis for the development of any DR, BDR and RDR

	Any DR (773)			BDR (729)		RDR (44)	
	n	Crude hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)	Crude hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)	Crude hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)
Duration of diabetes							
≤10 years	1,295	1.00	1.00	1.00	1.00	1.00	1.00
11-19 years	298	1.83 (1.54, 2.17)	1.80 (1.51, 2.15)	1.80 (1.51, 2.16)	1.79 (1.49, 2.14)	2.25 (1.05, 4.57)	2.24 (1.10, 4.58)
≥20 years	203	1.86 (1.52, 2.26)	2.84 (1.50, 2.24)	1.79 (1.45, 2.19)	1.77 (1.44, 2.18)	2.65 (1.28, 5.51)	2.38 (1.14, 4.97)
Age at diagnosis of diabetes:							
≤10 years	371	1.00	1.00	1.00	1.00	1.00	1.00
11-20 years	491	0.70 (0.57, 0.86)	0.73 (0.59, 0.89)	0.69 (0.56, 0.85)	0.71 (0.58, 0.88)	0.69 (0.32, 1.52)	0.74 (0.34, 1.62)
>30 years	934	0.74 (0.62, 0.87)	0.74 (0.62, 0.88)	0.75 (0.63, 0.90)	0.74 (0.61, 0.88)	0.51 (0.25, 1.04)	0.54 (0.27, 1.10)
Gender:							
Male	971	0.91 (0.79, 1.05)	0.98 (0.85, 1.13)	0.94 (0.81, 1.08)	1.00 (0.87, 1.16)	0.45 (0.24, 0.84)	0.51 (0.27, 0.95)
Female	818	1.00	1.00	1.00	1.00	1.00	1.00

any DR - any diabetic retinopathy; BDR - background diabetic retinopathy; RDR - referable diabetic retinopathy; 95% CI - 95% confidence interval;

4.4.2.3 Screening intervals

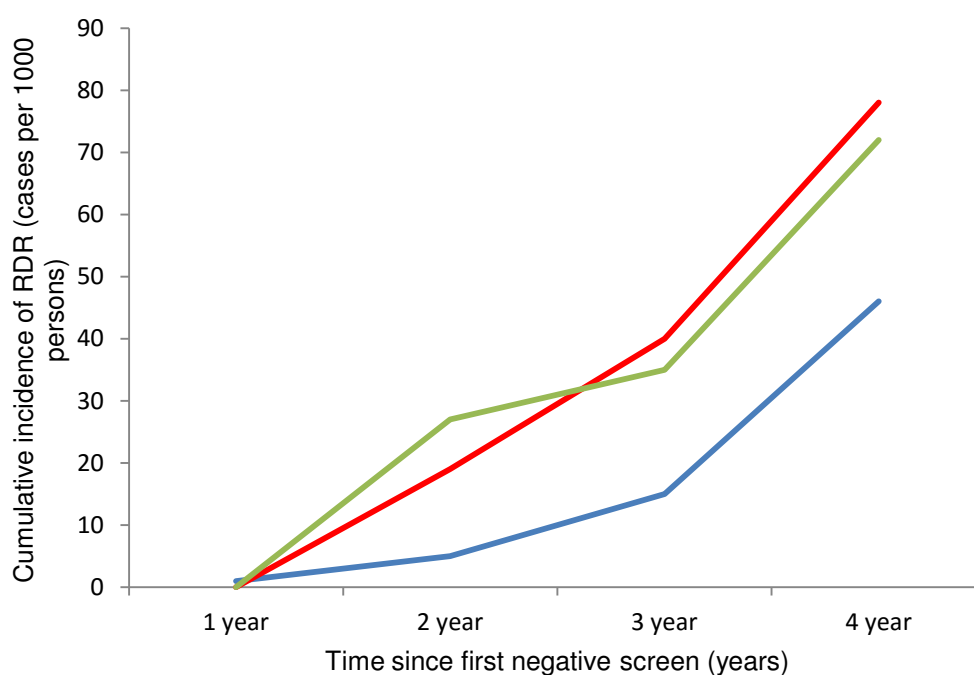
As duration of diabetes was shown to be the most important putative risk factor for DR of the ones available, it was subsequently used to assess the cumulative incidence of RDR. This was done in order to examine the impact of different stratifications based on duration of diabetes and differing screening intervals (Figure 4.4.10).

In persons with a duration of diabetes of ≤ 10 years there was 1 case of RDR per 1,000 persons one year after an initial negative screening event which increased to 5 cases after two years and 15 cases after three years. When the duration of diabetes was 11 to 19 years surprisingly there were no cases of RDR in the first year following a negative screening event. However, two years later there were 19 cases and the number increased to 40 after three years. In those persons with a duration of diabetes ≥ 20 years again surprisingly there were no cases of RDR in the first year following a negative screening, however this increased to 27 cases after two years and 35 cases after three years.

Screening intervals in persons with T1DM could be extended to once every two years with only a small increased risk in delaying the diagnosis of RDR (1 case per 1,000 persons), as there were no cases of RDR in persons with a duration of diabetes of 11-19 years or ≥ 20 years. If the screening interval was increased to once every three years, 6 cases would be at risk of a delay in referral for those with a duration of diabetes of ≤ 10 years. The risk increased by 3.8 fold for those with a duration of diabetes between 11 to 19 years, and 5.8 times for those with diabetes ≥ 20 years. Therefore a screening interval of once every three years could be appropriate for those with T1DM with a duration of diabetes ≤ 10 years, if 6 cases

per 1,000 persons was deemed an appropriate level of risk, decreasing to biennial once the duration of diabetes exceeded 10 years.

Figure 4.4.10: Incidence of RDR by duration of diabetes over four years in persons with T1DM



	Category	Total n	RDR cases n	Incidence of RDR*			
				*1 year	*2 years	*3 years	*4 years
—	≤10 years	1295	21	1	5	15	46
—	11-19 years	298	12	0	19	40	78
—	≥20 years	203	11	0	27	35	72

*Incidence of RDR provided as cases per 1,000 persons.

4.4.2.4. Summary of main findings

- During a four year study period involving a population of 1,749 persons with T1DM, without evidence of DR at their first screening event by the DRSSW, a total of 3 persons developed PDR. These 3 persons were younger at diagnosis of diabetes with a longer duration of diabetes compared to those who did not develop PDR.
- A Surprising finding was that 50% of those who developed RDR had maculopathy without evidence of PPDR or PDR.
- The four year cumulative incidence of any DR, BDR and RDR was 649, 635 and 56 cases per 1,000 persons.
- Duration of diabetes, when adjusted for age at diagnosis and gender, was the most significant predictor for the incidence of any DR, BDR and RDR.
- All persons with T1DM without evidence of DR could be placed on a biennial screening interval with only 1 case per 1,000 persons at risk of a delay in referral to the HES.
- If the screening interval was adjusted based on duration of diabetes then for those persons with a duration of diabetes of ≤ 10 years 6 cases per 1,000 persons would be at delayed diagnosis of RDR if the screening interval were extended to triennial for this group. However, due to the small population size and dropouts these findings should be interpreted with caution.

4.5 Discussion

This study involved a large population of 49,763 persons with T2DM and a smaller population of 1,796 persons with T1DM without DR at their first screening event by the DRSSW. The four year cumulative incidence of any DR, BDR and RDR was

lower in persons with T2DM 445, 438 and 16 cases respectively per 1,000 persons compared to 649, 635 and 56 cases per 1,000 persons with T1DM respectively. Surprisingly, 50% of those with T1DM who developed RDR had maculopathy without PPDR or PDR. The proportion was only slightly higher at 57% of persons with T2DM. Maculopathy is usually more prevalent in persons with T2DM with PDR more prevalent in T1DM.(Klein et al. 1984)

Direct comparison between our study and that of others reporting incidence rates is difficult for reasons stated earlier (see Chapter 3) predominantly due to differences in classification of diabetes and DR grading protocols employed and technologies to visualise and record the retina image as well as the use of different statistical methods to measure and report incidence (i.e. parametric vs. non parametric tests and cases per 1,000 persons vs. percentages). However, some comparison of incidence rates can be made with two key studies i.e. the UKPDS, and the WESDR.(Klein et al. 1989a, b, Stratton et al. 2001) The four year cumulative incidence of any DR in persons with T2DM was higher in our study at 44.5% compared to 38.6% (386 cases per 1,000 persons) in those aged 30 years or more at diagnosis of diabetes in the WESDR study.(Klein et al. 1989b) Similarly the four year cumulative incidence of any DR was also higher at 65% in persons with T1DM in our study than that seen in the WESDR at 59% (590 cases per 1,000 persons) in persons less than 30 years of age.(Klein et al. 1989a) This may also reflect differences in population demographics. Our four year incidence rate at 44.5% were also slightly higher than the 6 year incidence rate of any DR at 41% (410 cases per 1,000 persons) seen in the newly diagnosed T2DM persons included in the UKPDS.(Stratton et al. 2001)

Two studies from screening programmes in the UK (Norfolk and Liverpool) provided incidence rates comparable to our study.(Younis et al. 2003a, Younis et al. 2003b,

Jones et al. 2012) The Norfolk screening programme of 16,444 persons predominantly with T2DM the four year cumulative incidence of RDR was higher at 3.7% or 37 cases per 1,000 persons comprising of PPDR 2.6%, maculopathy 0.5% and PDR 0.6% which is double the incidence of RDR in our study of persons with T2DM.(Jones et al. 2012) There were a small number of persons with T1DM included in the analysis of T2DM in the Norfolk study which may account for some of the higher rate seen compared to our study. In the Liverpool Eye Screening programme the four year cumulative incidence of sight-threatening DR was 2.1% in 3,743 persons with T2DM and 3.2% in 305 persons with T1DM,(Younis et al. 2003a, Younis et al. 2003b) which would equate to 21 cases per 1,000 persons with T2DM which is higher than the incidence of RDR that we observed. However, the 32 cases per 1,000 persons with T1DM was lower than RDR seen in our T1DM population. In addition to the different methods used to calculate the incidence rates there were also differences between the definition of RDR and sight-threatening DR as well as subtle differences in the grading protocols used, which could well account for these relatively small differences in the incidence rates estimated. In other population based studies (Chen et al. 1995, Gomes et al. 2000, Leske et al. 2003, Looker et al. 2003, Manaviat et al. 2008, Tam et al. 2008, Varma et al. 2010, Song et al. 2011) the four year incidence of any DR has mainly been reported in populations with T2DM or mixed T2DM and T1DM populations ranging from 15.2% in persons with T2DM in Hong Kong (Song et al. 2011) to 47.5% in persons with T2DM in Iran (Manaviat et al. 2008).

In our study the annual incidence of any DR and BDR fluctuated over the four years which may be due to the population sizes involved and the non-parametric method used to estimate the incidence rate. The Cox regression model assumes a constant hazard rate over a full study period, whereas in reality the hazard rates for the development of DR would be expected to increase over time which means that the

incidence of DR could be underestimated initially and then over estimated in the later stages or vice versa. (Kleinbaum et al. 2010) To illustrate this in the population of T2DM examined here using the Weibull regression analysis the four year cumulative incidence of any DR was 360 cases per 1,000 persons which was lower than calculated in this chapter of 445 cases using the Kaplan Meier method. (Thomas et al. 2012) However, Kaplan Meier and Cox regression analysis are more commonly used in health related research. The reason for this is no assumptions about the underlying nature or shape of the survival distribution are required and closely approximate the results for the correct parametric model.

The incidence of any DR, BDR and RDR was strongly associated with increasing duration of diabetes in persons with T2DM or T1DM after controlling for age at diagnosis of diabetes and gender, and treatment of diabetes in only those with T2DM. For those with T2DM for 10 years or more there was a 1.6 fold increased risk of any DR and 1.5 fold increased risk of RDR over the study period compared to those with diabetes for <5 years. In comparison those persons with T1DM for 20 years or more had a 2.8 fold increased risk of any DR and 2.4 fold increased risk of RDR compared to those with diabetes for 10 years or less. Similarly almost all DR studies of prevalence and incidence of DR have found duration of diabetes to have the strongest association with DR. (Younis et al. 2003b, Tapp et al. 2006, Cikamantana et al. 2007, Varma et al. 2007, Zhang et al. 2011)

In persons with T2DM in this study there was also a strong association for insulin therapy and the incidence of any DR, BDR and RDR. Relative to those on diet treatment only, those on diet plus OHAs had a 1.3 fold increased risk of any DR and BDR and a 1.5 fold increased risk of RDR. The risk relative to diet only treatment increased further for those on insulin therapy to 1.9 fold for any DR and BDR and

2.4 fold for RDR. This increased risk associated with the use of insulin therapy in persons with T2DM has been shown in previous incidence studies (Younis et al. 2003b, Jones et al. 2012) and in studies involving the initiation of insulin therapy in T2DM.(Roysarkar et al. 1993, Henricsson et al. 1995, Chantelau et al. 1997, Henricsson et al. 1997) This may reflect the prolonged period of poor glycaemic control prior to the initiation of therapy, with the possibility of the additional impact of a rapid improvement in control at the initiation of insulin therapy.(Zhao et al. 2014)

Although the cumulative incidence of RDR was low in our population over the four year study period, the cumulative incidence (cases per 1,000 persons) at 1 and 2 years preceded by a negative screening event was 0 and 3 cases with T2DM and 1 and 9 cases with T1DM respectively. The incidence of RDR varied considerably between subgroups, according to duration of diabetes in both T2DM and T1DM and treatment modality in persons with T2DM. In persons with T2DM and a known duration of <5 years on diet therapy only, the two year cumulative incidence was 3 cases rising to 11 cases when known duration increased to ≥ 10 years and on insulin therapy. In persons with T1DM for ≤ 10 years the two year cumulative incidence of RDR was 5 cases rising to 19 cases when duration increased to 11 to 19 years and to 27 cases with duration of ≥ 20 . However, the number of persons with T1DM within this study were low especially so for those who developed RDR and so any interpretation of these findings should be done with caution. 'Referable' disease should not be confused with 'treatable' disease where numbers would be even smaller as the majority of RDR are for changes near the fovea without any macular oedema.(Leese 2013) The potential visual implications of delaying the diagnosis of macular oedema are less than delaying the diagnosis of PDR.

Therefore, if the screening interval could be extended to once every two years for those with T2DM using insulin therapy with a duration of diabetes of ≥ 10 years and once every three years in those on diet only or using OHAs and insulin therapy with a duration of diabetes < 10 years. All persons with T1DM could be screened once every two years, however the risk may be too high to increase the screening interval beyond this.. This is in agreement with other UK screening programmes (Younis et al. 2003a, Younis et al. 2003b, Jones et al. 2012, Looker et al. 2013, Stratton et al. 2013, Looker et al. 2014) Most recently a report from the 4 Nations committee found that in persons with no evidence of DR in both eyes at two consecutive annual screening events, an appropriate yield of RDR of 2.5% would allow a recommendation for the screening interval to be extended to 2-3 years.(Four Nations Study Group 2013) However, two important caveats within the report were; a robust IT system, in order to prevent the loss of patients from the service and ensuring accurate and consistent grading without with such a recommendation would be unsafe. This evidence is currently being considered by the UK national screening committee.

Screening intervals have already been extended in some programmes across Europe and the US, although these countries use ophthalmologists or optometrists to conduct detailed evaluations of the retina through slit lamp biomicroscopy or digital retinal images. In Sweden, 1,691 persons with T2DM, good glycaemic control (mean HbA_{1c} of 6.4%) and relatively short duration of diabetes (mean 6 years) without DR were placed on a triennial screening interval. After 3 years only three persons developed maculopathy and none had developed severe non-proliferative DR or proliferative DR.(Agardh et al. 2011) In Iceland persons without DR are screened biennially and 296 persons (97 T1DM and 199 T2DM) with a mean duration of 18 years and HbA_{1c} 8.0% were followed over a period of 10 years. No person went from no DR to sight-threatening DR within a two year period. Of

the 33 persons who developed PPDR or worse or CSMO, all had developed mild non-PDR first and were therefore on an annual screening protocol prior to sight-threatening DR developing.(Olafsdottir et al. 2007) Both of these studies, although not providing incidence rates, highlight that it is possible to safely extend screening intervals to bi- or triennial without increasing the risk of a delayed diagnosis of DR requiring referral to HES in those with no DR at initial screening. In 2010, the American Diabetes Association recommended less frequent than annual screening in cases with at least one previous negative screening event.(Lundstrom et al. 2011) However, these guidelines were for a detailed evaluation of the retina to be conducted by an ophthalmologist or optometrist experienced in diagnosing DR.

In addition to these reports one cost effectiveness study was conducted in Exeter, which found that in persons with T2DM without DR an extension of the screening interval to once every two years was associated with a 25% reduction in costs without increasing the risk of vision loss.(Chalk et al. 2012)

Direct evidence from other UK screening programmes and related clinical trials has already been used to revise screening intervals for different types of cancer e.g. cervical (Sasieni et al. 2003), breast (The Breast Screening Frequency Trial Group 2002) and bowel (Mandel et al. 1993) screening programmes. Our study provides strong evidence from a large national screening programme that the annual screening interval could be extended in persons without DR, in both T2DM and T1DM without causing an increased risk of visual loss and blindness.

The limitations of this study was the restriction to two 45° retinal images per eye, and only limited information available on putative risk factors for the development of DR. This study also did not have access to measures of glycaemic control, blood pressure, and lipid concentrations. There was also a high dropout rate experienced

of 14.9% of participants who did not have a second screening event despite being eligible. This was especially a problem in the T1DM population, where numbers were already small. Information regarding those persons who did not participate in screening was also unobtainable; some may have been excluded for medical reasons or because they were already receiving care from an ophthalmologist for DR (an exclusion criteria for screening), or they did not attend for other unknown reasons. The use of Cox proportional hazards regression instead of more sensitive parametric models such as Weibull may also be a limitation in this study. However, Cox regression is widely used in medical research and its findings are robust and closely approximate to the correct parametric model. (Kirkwood et al. 2003) Using the grade of retinopathy from the worst eye only and based on the first screening event may also be a limitation of this study. The use of two consecutive negative screening events and based on individual eyes as reported in the four nations diabetic retinopathy screening intervals project and in Scotland by Looker et al may provide a group at an even lower risk of development of RDR and therefore allow a safer extension of the screening interval. (Four Nations Study Group 2013, Looker et al. 2013)

4.5.1 Summary of main findings

- In persons with diabetes without evidence of DR at initial screening there was a very low incidence of RDR in persons with both T2DM and T1DM after one year.
- The incidence of RDR varied considerably between subgroups with those with T2DM for 10 years or more and using insulin therapy and in persons with T1DM for 20 years or more having the highest incidence.

- The screening interval could reasonably be extended to once every two years for all persons with diabetes who have no evidence of DR at their first screening event.
- Furthermore, it may be possible to extend the screening interval to once every three years in those with T2DM of less than 10 years and not receiving insulin therapy.

Chapter 5

Prevalence of diabetic retinopathy, visual impairment and putative risk factors at time of first screening event - Centre for Diabetes and Endocrinology (CDE), Johannesburg, South Africa 2001-2010

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5.1 Introduction

The country of South Africa has an estimated population of approximately 52 million, with the vast majority being indigenous Africans (79.5%) and a much smaller minority comprising of mixed races (9%), Caucasians (9%), and Asian Indians (2.5%).(U.S. Department of State 2011) It is located at the southern tip of Africa and is divided into 9 provinces. It is considered an emerging economy, however, approximately a quarter of the country's population are unemployed.(www.gov.za 2014) The health care system in South Africa consists of a large and under-resourced public sector, and a smaller fast growing private sector. Health care varies from basic primary health care, which is provided free by the state for approximately 80% of the population, to highly specialised services available in the private sector.(www.safic.info 2011) Approximately 80% of medical doctors employed in South Africa work only in the private sector.

It has been estimated that the prevalence of diabetes in South Africa is 8.3% of the population (International Diabetes Federation 2014), with only 11% of those with diabetes having their eyes routinely examined for DR.(Read et al. 2007) Diabetes is the fourth leading cause of blindness in South Africa (after cataract, glaucoma and age related macular degeneration)(Cockburn et al. 2012) and accounts for 8,000 new cases of visual impairment every year.(Hofman et al. 2014) There is evidence to suggest that the risk of DR and blindness in South Africa varies according to ethnicity.(West et al. 1982, Ross et al. 2007, Stolk et al. 2008, Raymond et al. 2009) This in part may be due to increased prevalence of diabetes and additional putative risk factors for DR or as yet unidentified reasons. In 2010, the global prevalence of DR was estimated to be 55.8% in African Americans, 46.7% in Caucasians, and 20.9% in Asian Indians.(American Diabetes Association 2010) In comparison, the

reported prevalence of DR in persons with diabetes in South Africa's public health care sector, based on minimal reports, indicate that DR is present in between 14 and 55% of Indigenous Africans, 41% of Caucasians, and 22 and 37% of Asian Indians.(Kalk et al. 1997, Levitt et al. 1997, Carmichael et al. 2005)

In 2002, South Africa signed up to Vision 2020 and published its national guidelines for the prevention of blindness.(World Health Organisation 2000, Department of Health 2002, World Health Organisation 2007, 2013) Both documents include recommendations for the provision of screening for DR. However, screening in the public sector is difficult in South Africa, as resources are already overstretched, and could not cope with the increased demands resulting from the identification of sight-threatening DR requiring further assessment and treatment by screening.(Mash et al. 2007, Cook 2013) Where screening exists it is adhoc and opportunistic, and systematic screening is unlikely in the near future.(Cook et al. 2014) Those persons able to access private health care in South Africa are from a higher socioeconomic background than those in the public sector. The prevalence of DR in the much smaller private health care sector (with its different ethnic distribution) has not previously been reported prior to this study.(Thomas et al. 2013) This dataset which was provided to us by Dr Larry Distiller (CDE) was an unique opportunity to analyse the association between DR and a more extensive range of putative risk factors than were available to us at the DRSSW and traditionally collected by screening programmes in the UK.

5.2 Aims

The primary aim of this study was

- to determine the prevalence of any DR, BDR and RDR within the population attending the CDE, a private healthcare provider, on the occasion of their first screening visit and
- to determine if the presence of any DR, BDR or RDR varied according to ethnicity

The secondary aims of this study was

- to investigate the impact of putative risk factors (glycaemic control, duration of diabetes, hypertension and dyslipidaemia) on the prevalence of any DR, BDR and RDR
- to determine the prevalence of visual impairment and blindness within the CDE at first screening
- to determine the risk factors associated with visual impairment and blindness

5.3 Methods

Retinal Screening

All persons with diabetes attending the CDE in Johannesburg, South Africa, undergo routine digital retinal photography performed at the time of their first visit and annually thereafter. All details of screening and grading protocols are provided in Chapter 2. In brief, screening consisted of visual acuities recorded using a 3m illuminated Snellen chart, digital retinal photography using a Canon CR6 non-mydratic camera capturing one central 45° macular image per eye without the use of

mydriasis. All the retinal images were internally graded at the CDE, but were re-graded by one of three accredited graders according to the DRSSW grading protocol.

Clinical laboratory data

At the time of initial presentation, when the first retinal photographs were taken, blood and urine samples were obtained for baseline laboratory investigations including HbA_{1c}, fasting lipid analyses (total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides), serum creatinine, urinary albumin excretion. The Albumin:Creatinine ratio (ACR) was estimated and resting supine blood pressure and use of anti-hypertensive medication was recorded.

Statistical Methods

The methods of screening data cleaning and statistical analysis used within this chapter are described in detail in Chapter 2. In this chapter, variables (age at diagnosis of diabetes, duration of diabetes, gender, ethnicity, glycaemic control, total cholesterol, ACR, smoking status, hypertension, and the use of ACE inhibitors or aspirin therapies) were assessed for their association with the presence of any DR, BDR and RDR using binary univariate and backwards stepwise multivariate logistic regression analyses. All continuous variables were stratified to avoid assumptions of linearity (Table 5.3.1).

Table 5.3.1: Stratification of continuous variables

		T1DM (n)	T2DM (n)
Total Chol (mmol/L)	Low	<5 (1,092)	<5 (2,666)
	High	>5 (417)	>5 (1,256)
ACR (mg/mmol)	Low	<3 (1,405)	<3 (3,568)
	High	>3 (131)	>3 (405)
HbA _{1c} (%)		<7 (310)	<6.6 (966)
		7.0 -7.9 (342)	6.6-7.4 (1,097)
		8.0-8.9 (322)	7.5 -8.9 (1,008)
		>9 (563)	>9 (907)
Duration of diabetes (years)		<7 (505)	<3 (1,391)
		7-15 (515)	3-8 (1,360)
		>15 (517)	>8 (1,224)
Age at diagnosis (years)		<14 (519)	<46 (1,403)
		14-26 (471)	46-55 (1,265)
		>26 (540)	>55 (1,286)

ACR - albumin creatine ratio; Total chol - total cholesterol

5.4 Results

5.4.1 Diabetic retinopathy

Prevalence of diabetic retinopathy within the total population

A total of 5,565 persons were screened for DR at the CDE in Johannesburg between 2001 and 2010. The majority of persons had T2DM (71.5%) with 27.6% having T1DM. The remaining 0.9% were excluded from all subsequent analysis as they had IGT or other forms of diabetes, such as latent autoimmune diabetes of adulthood (LADA). The majority of the total CDE population (5,515) who were included in the study were male (63.4%), and Caucasian (71.2%) (Table 5.4.1). The mean age of the study population was 51 years, duration of diabetes 9 years and they had a mean age at diagnosis of diabetes of 42 years. The mean HbA_{1c} of the population at baseline was 8.0%, total cholesterol 5.0 mg/dl and ACR was 4.3 mg/mmol. Almost 20% were smokers, with approximately 40% being hypertensive (34% on ACE inhibitors).

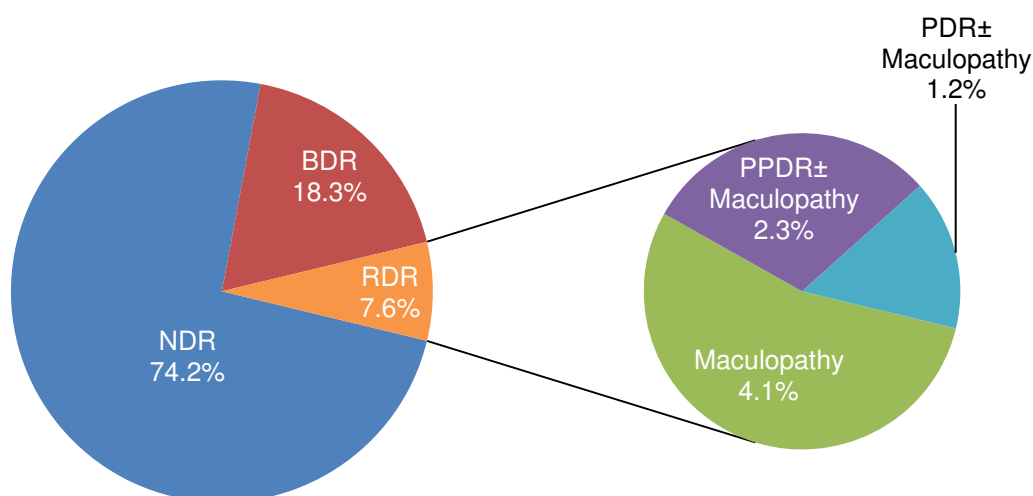
Table 5.4.1: Characteristics of the study population at first screening (baseline)

	N=5,515
Age yrs mean (SD)	50.8 (16.1)
Gender: n (%)	
Male	3,496 (63.4)
Female	2,016 (36.6)
Ethnicity: n (%)	
Caucasian	3,909 (71.2)
Asian Indian	697 (12.7)
Indigenous African	680 (12.4)
Mixed Race	208 (3.8)
Type of diabetes: n (%)	
T1DM	1,537 (27.9)
T2DM	3,978 (72.1)
Duration of diabetes yrs mean (SD)	8.5 (8.6)
Age at diagnosis of diabetes yrs mean (SD)	42.3 (17.6)
HbA _{1c} % mean (SD)	8.2 (2.0)
Total Cholesterol mmol/L mean (SD)	5.0 (1.2)
ACR mg/mmol mean (SD)	0.1 (0.3)
Smoking n (%)	909 (16.5)
Hypertensive n (%)	2,428 (44.0)
ACE inhibitors n (%)	1,873 (34.0)
Aspirin n (%)	787 (14.3)

yrs - years; SD - standard deviation; n - number; ACR - albumin creatinine ratio; ACE - angiotensin converting enzyme inhibitors;

The overall prevalence of any DR within the total study population was 25.9% (95% CI 24.7, 27.0) (Figure 5.4.1) with no evidence of DR in 74.2% (95% CI 73.0, 75.3). Of those with DR, BDR was evident in 18.3% (95% CI 17.3, 19.4) and RDR in 7.6% (95% CI 6.9, 8.3). RDR comprised of 0.88% (95% CI 0.66, 1.2) with PPDR; 4.1% (95% CI 3.6, 4.7) with maculopathy; 1.4% (95% CI 1.1, 1.8) with PPDR and maculopathy; 0.44% (95% CI 0.29, 0.66) PDR; and 0.72% (95% CI 0.53, 0.99) with PDR and maculopathy. There were 4.8% (95% CI 4.2, 5.4) with ungradeable images predominantly due to media opacification.

Figure 5.4.1: Prevalence of DR in persons with diabetes attending the CDE, South Africa



NDR - no diabetic retinopathy; BDR - background diabetic retinopathy; RDR - referable diabetic retinopathy; PPDR - preproliferative diabetic retinopathy; PDR - proliferative diabetic retinopathy

5.4.1.1 T2DM

5.4.1.1.1 Prevalence of DR in persons with T2DM

There were a total of 3,978 persons with T2DM within the CDE diabetes management programme. The characteristics of the population at baseline (first screening event) are represented in Table 5.4.2. The majority (two thirds) of those with T2DM were male and of Caucasian origin. The mean age was 56.6 years, median known duration of diabetes was 5.0 years and the mean HbA_{1c} level was 7.5%. From here on known duration of diabetes in persons with T2DM will be referred to as duration.

Table 5.4.2: Characteristics of persons with T2DMat first screening.

Characteristics	T2DM (n=3,978)
Age yrs mean (SD)	56.8 (11.8)
Gender n (%):	
Male	2,650 (66.6)
Female	1,326 (33.3)
Ethnicity n (%):	
Caucasian	2,662 (66.9)
Indigenous African	580 (14.6)
Asian Indian	562 (14.1)
Mixed Race	159 (4.0)
Duration of diabetes yrs median (IQ)	5.0 (1.0 to 10.0)
Age at diagnosis diabetes yrs mean (SD)	50.1 (11.8)
HbA _{1c} % median (IQ)	7.5 (6.6 to 8.9)
Total Cholesterol mmol/L mean (SD)	5.0 (1.2)
ACR median (IQ)	1.1 (0.5 to 3.6)
Other therapies:	
ACE n (%)	1,620 (40.7)
Aspirin n (%)	743 (18.7)
Hypertensive n (%)	2,441 (53.8)
Smoker n (%)	607 (15.3)

ACR - albumin creatinine ratio; ACE - angiotensin converting enzyme; yrs - years; n - numbers; IQ - interquartile range; SD - standard deviation

Caucasian persons were older at baseline ($p<0.001$) and at the time of diagnosis of diabetes ($p<0.001$) with a lower HbA_{1c} ($p<0.001$) than non-Caucasians (Table 5.4.3). The duration of diabetes was similar across all the ethnic groups included. There were significant differences in gender distribution across the ethnicities with more males of Caucasian origin compared to indigenous Africans, Asian Indians and those of a Mixed Race ($p=0.008$) and more females of Mixed Race compared to Indigenous Africans, Asian Indians and Caucasians ($p<0.013$).

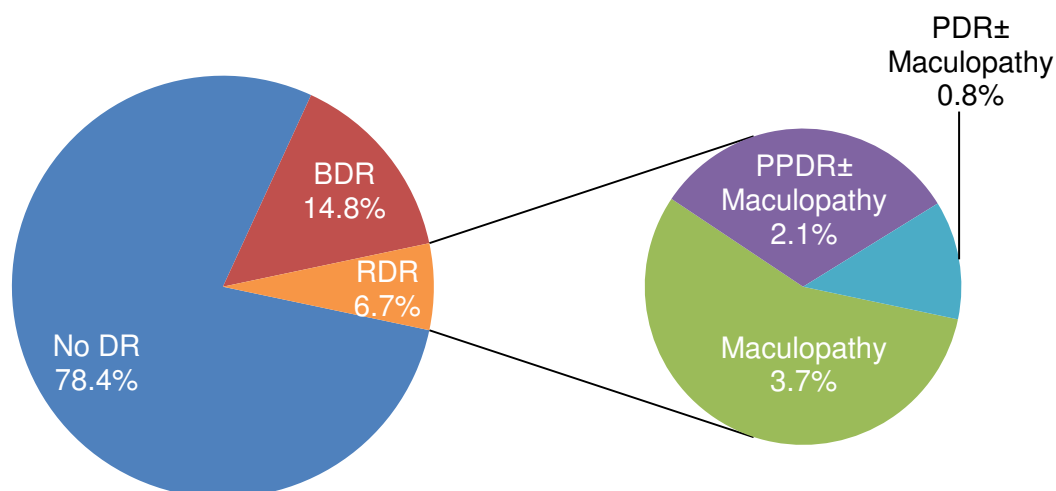
Table 5.4.3: Baseline characteristics of different ethnic groups in persons with T2DM

	Caucasian (n=2,662)	Indigenous African (n=580)	Asian Indian (n=562)	Mixed Race (n=159)	P value
Age yrs mean (SD)	59.7 (11.1)	51.7 (10.0)	50.5 (11.8)	49.5 (10.7)	0.037
Gender: n (%)					
Male	1,810 (68.0)	382 (65.9)	362 (64.4)	85 (53.5)	0.013
Female	851 (32.0)	197 (34.0)	200 (35.6)	74 (46.5)	
Duration of diabetes yrs median (IQ)	5.0 (1.0 to 10.0)	5.0 (2.0 to 10.0)	5.0 (1.0 to 10.0)	4.0 (1.0 to 10.0)	0.173
Age at diagnosis of Diabetes yrs mean (SD)	53.0 (11.4)	44.6 (9.8)	43.5 (11.5)	43.7 (10.3)	0.199
HbA _{1c} % median (IQ)	7.3 (6.5 to 8.4)	8.3 (7.0 to 10.5)	7.9 (6.9 to 9.4)	8.1 (7.0 to 10.0)	0.003

yrs - years; n - numbers; IQ - interquartile range; SD - standard deviation

The prevalence of any DR in those persons with gradeable images was 21.6% (95% CI 20.3, 22.9) with no DR detected in 78.4% (95% CI 77.1, 79.7, n = 2,968) (Figure 5.4.2). The majority of DR seen was BDR 14.8% (95% CI 13.7, 15.9, n = 561) with 6.7% (95% CI 5.9, 7.5, n = 255) having RDR. The category of RDR consisted of 0.7% (95% CI 0.5, 1.0 n = 28) PPDR; 3.7% (95% CI 3.1, 4.3, n = 141) maculopathy; 1.4% (95% CI 1.0, 1.8, n = 54) PPDR with maculopathy; 0.2% (95% CI 0.1, 0.4, n = 8) PDR; and 0.6% (95% CI 0.4, 0.9, n = 24) PDR with maculopathy. There were an additional 4.8% with ungradeable images (95% CI 4.3, 5.6) possibly due to media opacifications, the cause of which could not be determined as no external images were provided and no details were given by clinician.

Figure 5.4.2: Prevalence of DR in persons with T2DM



No DR - no diabetic retinopathy; BDR - background diabetic retinopathy; RDR - referable diabetic retinopathy; PPDR - pre-proliferative diabetic retinopathy; PDR - proliferative diabetic retinopathy

5.4.1.1.2. Risk Factors for DR

Ethnicity

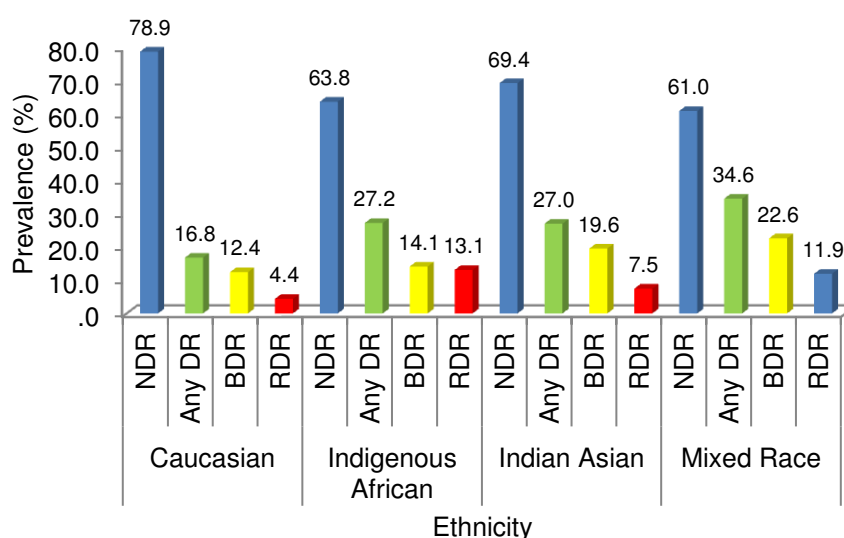
There was a lower proportion of Caucasians than all other ethnic groups in persons with any DR compared to those without DR (Table 5.4.4). The prevalence of any DR, BDR and RDR were lowest in Caucasians at 16.8%, 12.4% and 4.4% respectively, and whilst the prevalence of any DR and BDR were highest in those of Mixed Race at 34.6% and 22.6% the prevalence of RDR was highest in Indigenous Africans at 13.1% (Figure 5.4.3). This difference was significant when compared to those without DR (Table 5.4.4).

Table 5.4.4: Characteristics of persons with T2DM presenting without or with any DR, BDR and RDR

	NDR (n = 2,968)	Any DR (n=816)	P Value No DR vs. any DR	BDR (n=561)	RDR (n=255)	P value No DR vs. BDR and RDR
Age yrs mean (SD)	56.1 (11.9)	57.4 (11.0)	0.005	57.7 (11.5)	56.7 (10.0)	0.013
Gender: n (%)			0.816			0.182
Male	1,967 (66.3)	543 (66.7)		385 (68.8)	158 (62.2)	
Female	1,001 (33.7)	271 (33.2)		175 (31.2)	96 (37.8)	
Duration of diabetes yrs median (IQ)	3.0 (1.0-7.0)	10.0 (6.0-16.0)	<0.001	10.0 (5.0-15.0)	12.0 (8.0-17.0)	<0.001
Age at diagnosis yrs mean (SD)	51.1 (11.9)	45.8 (11.4)	<0.001	46.7 (11.8)	43.9 (10.2)	<0.001
Ethnicity: n (%)			<0.001			<0.001
Caucasian	2,100 (71.0)	448 (55.1)		331 (59.2)	117 (46.1)	
Indigenous African	370 (12.5)	158 (19.4)		82 (14.7)	76 (29.9)	
Asian Indian	390 (13.2)	152 (18.7)		110 (19.7)	42 (16.5)	
Mixed race	97 (3.3)	55 (6.7)		36 (6.4)	19 (7.5)	
HbA _{1c} % median (IQ)	7.3 (6.5-8.6)	8.2 (7.1-9.7)	<0.001	8.1 (7.0-9.4)	8.7 (7.6-10.4)	<0.001
Total Cholesterol	5.0 (1.2)	5.0 (1.2)	0.330	4.9 (1.1)	5.2 (1.3)	0.029
ACR	0.95 (0.49-2.7)	2.10 (0.7-7.7)	<0.001	1.4 (0.6-5.7)	4.8 (1.5-13.2)	<0.001
Smoker n (%)	463 (15.6)	125 (15.3)	0.844	94 (16.8)	31 (12.2)	0.239
Hypertensive n (%)	1,540 (51.9)	483 (59.2)	<0.001	324 (57.8)	159 (62.4)	<0.001
ACE n (%)	1,153 (38.8)	374 (45.8)	<0.001	253 (45.1)	121 (47.5)	0.001
Aspirin n (%)	569 (19.2)	138 (16.9)	0.143	96 (17.1)	42 (16.5)	0.333

No DR - no diabetic retinopathy; any DR - any diabetic retinopathy; BDR - Background diabetic retinopathy; RDR - referable diabetic retinopathy; n - number; yrs - years; SD - standard deviation; IQ - interquartile range; ACR - albumin creatinine ratio; ACE - angiotensin converting enzyme.

Figure 5.4.3: Prevalence of DR by ethnicity in persons with T2DM



The presence of any DR, BDR and RDR were also associated with ethnicity with those of a non-Caucasian origin at an increased risk compared to Caucasians (Table 5.4.5). Indigenous Africans were at a 2.0-fold increased risk of any DR at first screening, a 1.4-fold increased risk of BDR and a 3.7-fold increased risk of RDR compared to Caucasians. Asian Indians had an 1.8-, 1.8- and 1.9-fold increased risk of having any DR, BDR and RDR whereas those of a Mixed Race had a 2.7-, 2.4- and 3.5-fold increased risk respectively when compared to Caucasians. Once adjusted for age at diagnosis, known duration of diabetes and HbA_{1c} level those of Mixed Race remained at greatest risk of any DR, BDR and RDR at first screening compared to Caucasians with a 2.7-, 2.6- and 3.4-fold increased risk respectively (Table 5.4.6).

Table 5.4.5: Univariate logistic regression analysis for the presence of any DR, BDR and RDR at first screening in persons with T2DM

	Any DR OR (95% CI) n=816	BDR OR (95% CI) N=561	RDR OR (95% CI) n=255
Age at diagnosis yrs:			
<46 (1,403)	1.00	1.00	1.00
46-55 (1,265)	0.64 (0.54, 0.77)	0.71 (0.57, 0.87)	0.53 (0.39, 0.71)
>55 (1,286)	0.33 (0.27, 0.40)	0.40 (0.32, 0.51)	0.20 (0.13, 0.29)
Male (2,650)	1.02 (0.87, 1.20)	1.12 (0.92, 1.36)	1.19 (0.92, 1.56)
Ethnicity			
Caucasian (2,662)	1.00	1.00	1.00
Indigenous African (580)	2.00 (1.62, 2.48)	1.41 (1.08, 1.83)	3.69 (2.71, 5.02)
Asian Indian (562)	1.83 (1.48, 2.26)	1.79 (1.41, 2.28)	1.93 (1.34, 2.80)
Mixed Race (159)	2.66 (1.88, 3.76)	2.36 (1.58, 3.51)	3.52 (2.08, 5.95)
Duration of diabetes yrs			
<3 (1,391)	1.00	1.00	1.00
3-8 (1,360)	2.61 (2.02, 3.63)	2.68 (2.02, 3.57)	2.36 (1.41, 3.95)
>8 (1,224)	11.24 (8.84, 14.28)	9.19 (7.00, 12.07)	18.03 (11.47, 29.34)
HbA _{1c} %			
≤6.5 (966)	1.00	1.00	1.00
6.6-7.4 (1,097)	1.61 (1.25, 2.09)	1.58 (1.18, 2.11)	1.75 (1.05, 2.94)
7.5-8.9 (1,008)	2.77 (2.16, 3.55)	2.46 (1.86, 3.27)	3.84 (2.38, 6.18)
≥9.0 (907)	3.86 (3.01, 4.95)	2.99 (2.24, 3.97)	6.93 (4.37, 10.99)
Hypertension (2,141)	1.35 (1.15, 1.57)	1.27 (1.06, 1.52)	1.54 (1.18, 2.00)
Total Cholesterol			
>5mmol/l (1,256)	0.95 (0.81, 1.13)	0.94 (0.78, 1.15)	0.98 (0.74, 1.29)
ACR >3mg/mmol (405)	1.90 (1.51, 2.30)	1.56 (1.18, 2.07)	2.72 (1.96, 3.79)
ACE inhibitors (1,620)	1.33 (1.14, 1.56)	1.29 (1.08, 1.55)	1.42 (1.10, 1.84)
Aspirin (743)	0.86 (0.70, 1.05)	0.87 (0.69, 1.10)	0.83 (0.59, 1.17)
Smokers (607)	0.98 (0.79, 1.21)	1.09 (0.85, 1.39)	0.75 (0.51, 1.10)

Any DR - any diabetic retinopathy; BDR - background diabetic retinopathy; RDR - referable diabetic retinopathy; OR - odds ratio; 95% CI - 95% confidence interval; yrs - years; ACR - albumin creatinine ratio; ACE - angiotensin converting enzyme

Table 5.4.6: Multivariate logistic regression analysis for the presence of any DR, BDR and RDR at first screening in persons with T2DM

	Any DR OR (95% CI) n=816	BDR OR (95% CI) n = 561	RDR OR (95% CI) n=255
Age at diagnosis yrs			
<46 (n=1,403)	1.00	1.00	1.00
46-55 (n=1,265)	0.88 (0.72, 1.08)	0.91 (0.72, 1.14)	0.78 (0.56, 1.08)
>55 (n=1,286)	0.71 (0.56, 0.90)	0.75 (0.57, 0.97)	0.55 (0.35, 0.85)
Male (n=2,650)	1.04 (0.87, 1.26)	1.11 (0.90, 1.37)	0.85 (0.63, 1.14)
Ethnicity			
Caucasian (n=2,662)	1.00	1.00	1.00
Indigenous African (n=580)	1.78 (1.39, 2.28)	1.31 (0.98, 1.75)	3.08 (2.14, 4.43)
Asian Indians (n=562)	1.60 (1.26, 2.05)	1.60 (1.22, 2.10)	1.61 (1.07, 2.43)
Mixed Race (n=159)	2.68 (1.80, 4.00)	2.58 (1.65, 4.03)	3.35 (1.82, 6.16)
Duration of diabetes yrs			
<3 (n=1,391)	1.00	1.00	1.00
3-8 (n=1,360)	2.33 (1.79, 3.02)	2.42 (1.81, 3.24)	2.05 (1.21, 3.46)
>8 (n=1,224)	9.55 (7.43, 12.27)	8.03 (6.05, 10.65)	14.98 (9.37, 23.95)
HbA _{1c} %			
≤6.5 (n=966)	1.00	1.00	1.00
6.6-7.4 (n=1,097)	1.34 (1.01, 1.77)	1.31 (0.96, 1.78)	1.48 (0.86, 2.56)
7.5-8.9% (n=1,008)	1.85 (1.41, 2.42)	1.64 (1.22, 2.22)	2.47 (1.49, 4.09)
≥9.0 (n=907)	2.25 (1.71, 2.96)	1.86 (1.37, 2.54)	3.73 (2.28, 6.12)

Any DR - any diabetic retinopathy; BDR - background diabetic retinopathy; RDR - referable diabetic retinopathy; OR - odds ratio; 95% CI - 95% confidence interval; yrs - years;

Known duration of diabetes

The prevalence of any DR, BDR and RDR increased with increasing known duration of diabetes (Figure 5.4.4). In those with relatively newly diagnosed diabetes (known duration ≤2 years) the prevalence of any DR and RDR was 7.0%, and 1.6% respectively (Table 5.4.7). This increased to 29.6% and 9.9% respectively in those with a known duration of diabetes of 9-10 years. Once the known duration of diabetes had increased to 19-20 years the prevalence of any DR and RDR had increased to 57.6% and 17.4% respectively. Those persons presenting with any

DR, BDR or RDR had a significantly longer known duration of diabetes compared to those without DR (Table 5.4.4, page189).

Figure 5.4.4: Prevalence of diabetic retinopathy with increasing known duration of diabetes in person with T2DM

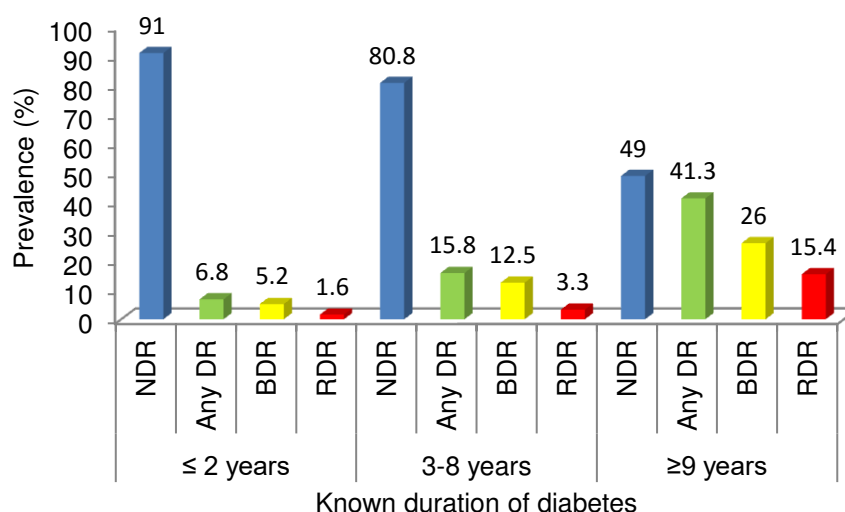


Table 5.4.7: The prevalence of any DR, BDR and RDR by known duration of T2DM.

Known Duration of diabetes (yrs)	n	Any DR % (95% CI)	BDR % (95% CI)	RDR % (95% CI)
0-2	1,361	7.0 (5.7, 8.5)	5.4 (4.3, 6.7)	1.6 (1.1, 2.4)
3-4	516	12.0 (9.5, 15.1)	8.7 (6.6, 11.5)	3.3 (2.1, 5.2)
5-6	468	16.0 (13.0, 19.6)	13.9 (11.1, 17.3)	2.1 (1.2, 3.9)
7-8	330	23.6 (19.4, 28.5)	18.2 (14.4, 22.7)	5.5 (3.5, 8.5)
9-10	335	29.6 (24.9, 34.7)	19.7 (15.8, 24.3)	9.9 (7.1, 13.5)
11-12	167	47.9 (40.5, 55.4)	29.9 (23.5, 37.3)	18.0 (12.9, 24.5)
13-14	109	51.4 (42.1, 60.6)	29.4 (21.6, 38.5)	22.0 (5.3, 30.7)
15-16	175	45.1 (38.0, 52.5)	25.4 (19.3, 32.1)	20.0 (14.8, 26.5)
17-18	60	66.7 (54.1, 77.3)	41.7 (30.1, 54.3)	25.0 (15.8, 37.2)
19-20	132	57.6 (49.1, 65.7)	40.2 (32.2, 48.7)	17.4 (11.9, 24.8)
21-22	26	76.9 (58.0, 89.0)	46.2 (28.8, 64.5)	30.8 (16.5, 50.0)
23-24	15	60 (35.8, 80.2)	26.7 (10.9, 52.0)	33.3 (15.2, 58.3)
25-28	34	67.7 (50.8, 80.9)	41.2 (26.4, 57.8)	26.5 (14.6, 43.1)
29+	53	45.3 (32.7, 85.6)	34.0 (22.7, 47.4)	11.3 (5.3, 22.6)

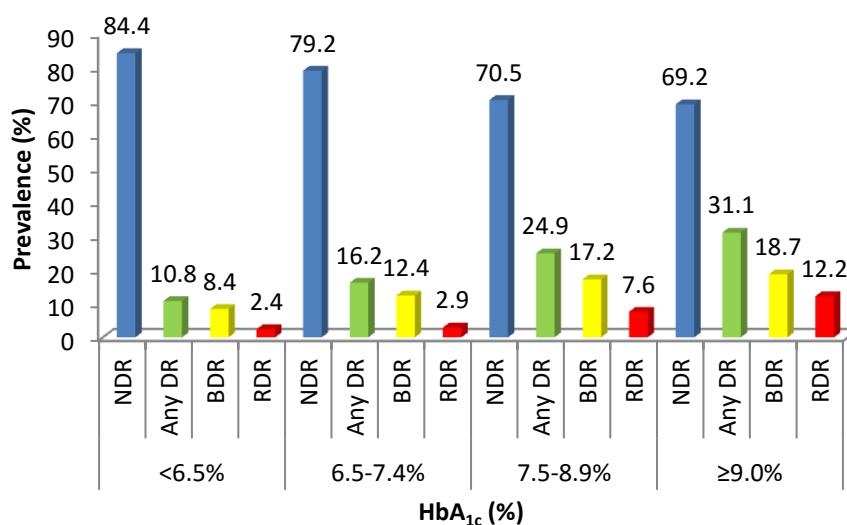
any DR - any diabetic retinopathy; BDR - background diabetic retinopathy; RDR - referable diabetic retinopathy; 95% CI - 95% confidence interval; yrs - years

Increased known duration of diabetes was strongly associated with the presence of any DR, BDR and RDR. In univariate analysis (Table 5.4.5, page 191), those with diabetes for 3-8 years had a 2.6-fold increased risk of having any DR, 2.7-fold for BDR and 2.4-fold for RDR, compared to those with diabetes for ≤ 2 years. This increased to 11.2-, 9.2- and 18.0-fold risk for those with diabetes duration of > 8 years. Once adjusted for age at diagnosis, ethnicity and HbA_{1c}, level the risk for those with diabetes for 3-8 years remained similar to that in the univariate analysis at 2.3-, 2.4- and 2.1-fold increased risk of having any DR, BDR and RDR respectively compared to those with diabetes for ≤ 2 years (Table 5.4.6, page 192). Whilst the risk decreased slightly in the fully adjusted model for those with diabetes for > 8 years to 9.6-, 8.0- and 15-fold increased risk compared to those with diabetes for ≤ 2 years.

Glycaemic Control

The prevalence of any DR, BDR and RDR increased with increasing HbA_{1c} (Figure 5.4.5). The prevalence of any DR was 2.8 times lower in persons with an HbA_{1c} of $< 6.5\%$ at 10.8% compared to those with an HbA_{1c} of $\geq 9.0\%$ at 31.1%. The prevalence of RDR was 5 times lower in persons with an HbA_{1c} of $< 6.5\%$ at 2.4% compared to an HbA_{1c} $\geq 9.0\%$ at 12.3%. Those with any DR, BDR and RDR had a significantly higher baseline HbA_{1c} level compared to those presenting without DR (Table 5.4.4, page 189).

Figure 5.4.5: Prevalence of DR by glycaemic control in persons with T2DM



Higher HbA_{1c} levels at baseline were associated with an increased risk of presenting with any DR, BDR and RDR (Table 5.4.5, page 191). Compared to those with HbA_{1c} levels of ≤6.5%, there was a 1.6-, 1.6-, and 1.8-fold increased risk of any DR, BDR and RDR at first screening respectively with HbA_{1c} 6.6-7.4%, 2.8-, 2.5- and 3.8-fold increased risk respectively with HbA_{1c} levels of 7.5-8.9% and a 3.9-, 3.0- and 6.9-fold increased risk respectively with HbA_{1c} levels of ≥9.0% in univariate analysis. Once adjusted for age at diagnosis, gender, known duration of diabetes and ethnicity these levels of risk decreased slightly in comparison to the univariate analysis but still remained significant (Table 5.4.6, page 192). Those with HbA_{1c} levels of 6.6-7.4% had a 1.3-, 1.3- and 1.4-fold increased risk of presenting with any DR, BDR and RDR compared to those with HbA_{1c} levels ≤6.5%. Those with HbA_{1c} levels of 7.5-8.9% had a 1.9-, 1.6- and 2.5-fold increased risk and those with HbA_{1c} levels of ≥9.0% had a 2.3-, 1.9- and 3.7-fold increased risk of having any DR, BDR or RDR respectively compared to those with a HbA_{1c} level ≤6.5%.

Other risk factors

In univariate analysis increasing ACR levels, a younger age at diagnosis, the presence of hypertension and the use of ACE inhibitors were associated with an increased risk of having any DR, BDR and RDR (Table 5.4.5, page 191). However, these factors were not maintained within the fully adjusted model, with the exception of age at diagnosis which was no longer significant.

5.4.1.1.3 Summary of main findings

In the study population persons with T2DM:

- The prevalence of any DR was 20.5%, BDR 14.1% and RDR was 6.4%
- In persons with diabetes duration of ≥ 20 years, 57.6% had any DR and 17.4% had RDR
- At an HbA_{1c} of $\leq 6.5\%$, 11.3% had any DR increasing to 33.1% with a HbA_{1c} of $\geq 9.0\%$. RDR was 2.5% at an HbA_{1c} of $\leq 6.5\%$ increasing to 13.2% at the higher levels of HbA_{1c} ($\geq 9.0\%$)
- Non-Caucasian ethnicity (compared to Caucasians) was independently associated with the presence of any DR, BDR and RDR with those of a Mixed Race at the greatest risk.
- Increased known duration of diabetes and an increasing HbA_{1c} were also independently associated with the presence of any DR, BDR and RDR following adjustment for confounders.

5.4.1.2 T1DM

5.4.1.2.1 Prevalence of DR

There were 1,537 persons with T1DM within the diabetes management programme at the CDE (Table 5.4.8). The mean age of this population was 35.4 years, the majority were male (55.0%) and Caucasian (81.1%). The median duration of diabetes was 11.1 years and HbA_{1c} was 8.4%. Those of Caucasian ethnicity were significantly younger at diagnosis of diabetes compared to the non-Caucasians i.e. Indigenous Africans, Asian Indian and those of a Mixed Race (21.6 vs. 28.5, 22.7, 22.7 years respectively) (Table 5.4.9). However, no other significant differences were seen.

Table 5.4.8: Baseline characteristics for all T1DM persons attending the CDE for their diabetes care

Characteristics	T1DM (n=1,537)
Age yrs mean (SD)	35.4 (15.4)
Gender n (%):	
Male	846 (55.0)
Female	690 (44.9)
Ethnicity n (%):	
Caucasian	1,247 (81.1)
Indigenous African	117 (7.6)
Asian Indian	118 (7.7)
Mixed Race	49 (3.2)
Duration of diabetes yrs median (IQR)	11.1 (5.0 to 19.0)
Age at diagnosis diabetes yrs mean (SD)	22.3 (13.8)
HbA _{1c} % median (IQ)	8.4 (7.3 to 9.8)
Total Cholesterol mmol/L mean (SD)	5.1 (1.1)
ACR median (IQ)	0.9 (0.4 to 2.1)
Other therapies:	
ACE n (%)	253 (16.5)
Aspirin n (%)	44 (2.6)
Hypertensive n (%)	287 (18.7)
Smoker n (%)	302 (19.6)

Key - yrs – years; SD – standard deviation; IQR – interquartile range;
ACE – angiotensin converting enzyme inhibitors; ACR - albumin creatinine ratio; n - number

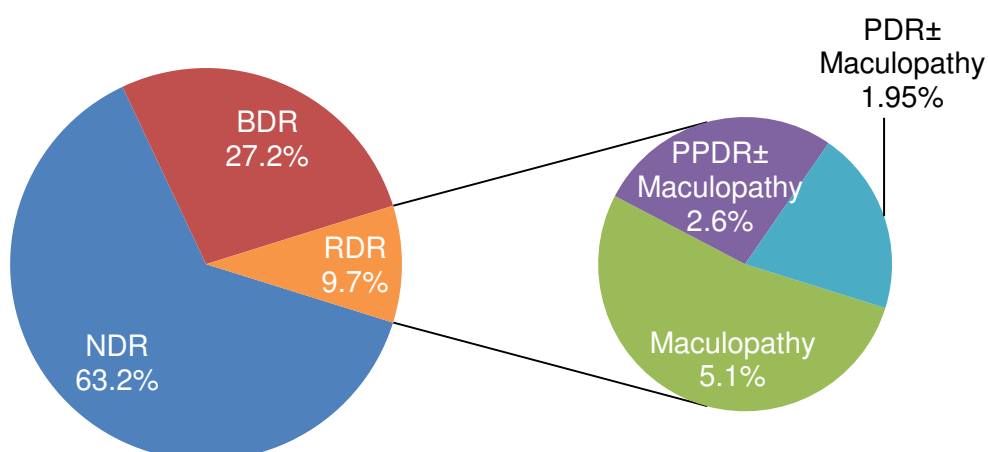
Table 5.4.9: Ethnic differences in baseline characteristics in persons with T1DM

	Caucasian (n=1,247)	Indigenous African (n=117)	Asian Indian (n=118)	Mixed Race (n=49)	P value
Age yrs mean (SD)	35.7 (15.6)	36.4 (16.1)	32.2 (12.1)	32.6 (15.2)	0.069
Gender: n (%)					
Male	690 (55.3)	66 (56.4)	65 (55.1)	21 (42.9)	0.253
Female	556 (44.6)	51 (43.6)	53 (44.9)	28 (57.1)	
Duration of diabetes yrs median (IQR)	2.0 (6.0 to 20.0)	5.0 (3.0 to 11.5)	8.0 (3.0 to 15.0)	8.0 (5.0 to 14.5)	0.070
Age at diagnosis of diabetes yrs mean (SD)	21.6 (13.6)	28.5 (15.5)	22.7 (11.8)	22.7 (14.6)	0.003
HbA _{1c} % median (IQR)	8.2 (7.3 to 9.6)	9.5 (7.8 to 11.3)	8.7 (7.6 to 10.9)	9.0 (7.3 to 11.4)	0.272

yrs - years; IQR - interquartile range; n - numbers;

In the T1DM population with gradeable images there were 63.2% (95% CI 60.7, 65.6) with no evidence of DR, 27.2% (95% CI 25.0, 29.5) with BDR and 9.7% (95% CI 8.3, 11.3) with RDR (Figure 5.4.6). The RDR category consisted of 1.2% (95% CI 0.8, 1.9) with PPDR; 5.1% (95% CI 4.1, 6.4) with maculopathy; 1.4% (95% CI 0.9, 2.1) with PPDR and maculopathy; 1.0% (95% CI 0.6, 1.7) PDR; and 0.95% (95% CI 0.57, 0.16) with PDR and maculopathy. Additionally there were 4.5% (95% CI 3.6, 5.6) with ungradeable images due to media opacification (this could not be analysed further).

Figure 5.4.6: Prevalence of DR in persons with T1DM



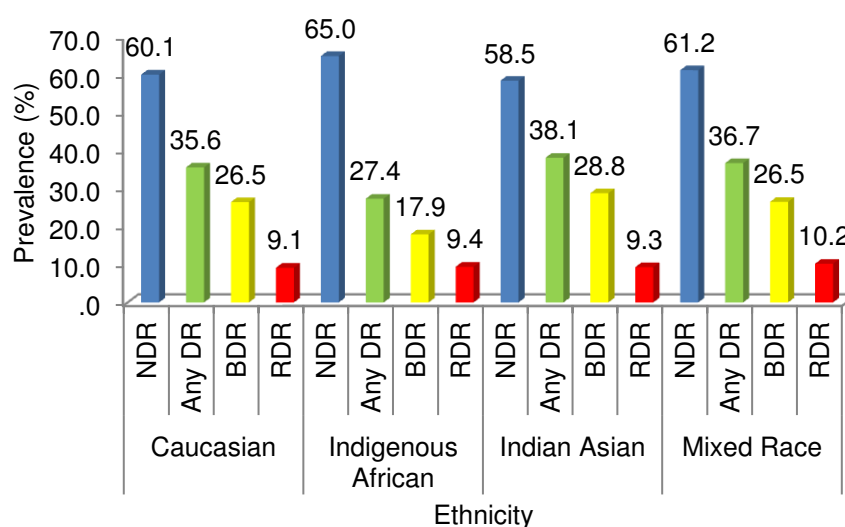
NDR - no diabetic retinopathy; BDR - background diabetic retinopathy; RDR - referable diabetic retinopathy; PPDR - preproliferative diabetic retinopathy; PDR - proliferative diabetic retinopathy

5.4.1.2.2 Risk Factors for DR

Ethnicity

The prevalence of any DR and BDR was lowest in Indigenous Africans and highest in Asian Indians (Figure 5.4.7), whereas the prevalence of RDR was similar across the four ethnic groups. There were no significant differences in ethnicity in those presenting with any DR, BDR or RDR when compared to those without DR (Table 5.4.10, page 197).

Figure 5.4.7: Prevalence of DR by ethnicity in persons with T1DM



NDR - no diabetic retinopathy; any DR - any diabetic retinopathy; BDR - background diabetic retinopathy; RDR - referable diabetic retinopathy

In univariate logistic regression analysis, ethnicity was not significantly associated with the presence of any DR, BDR or RDR (Table 5.4.11, page 198). However, ethnicity was retained in the multivariate logistic regression analysis after adjusting for gender, age at diagnosis, duration of diabetes, HbA_{1c}, current smoking status and the presence of hypertension (Table 5.4.12, page 199). Asian Indians were at an increased risk of any DR (OR 2.01) and BDR (OR 1.93) when compared with Caucasians. Also when compared with Caucasians, Indigenous Africans had an increased risk of RDR (OR 3.38).

Table 5.4.10: Characteristics of persons with T1DM presenting without DR or with any DR, BDR and RDR

	No DR (N = 927)	Any DR (n = 541)	P value No DR vs. Any DR	BDR (n = 399)	RDR (n = 142)	P value No DR vs. BDR and RDR
Age yrs mean (SD)	32.9 (15.6)	38.0 (14.0)	<0.001	37.8 (14.0)	38.6 (12.2)	<0.001
Gender: n (%)			0.329			0.363
Male	496 (53.6)	304 (56.2)		224 (56.1)	80 (56.3)	
Female	430 (46.4)	237 (43.8)		175 (43.9)	62 (43.7)	
Duration of diabetes yrs median (IQ)	6.0 (3.0-12.0)	17.0 (12.0-23.0)	<0.001	16.0 (11.0-22.0)	18.0 (14.0-25.0)	<0.001
Age at diagnosis yrs mean (SD)	23.5 (14.4)	19.6 (11.8)	<0.001	19.8 (12.0)	19.0 (11.4)	<0.001
Ethnicity: n (%)			0.418			0.692
Caucasian	749 (81.1)	444 (82.1)		330 (82.9)	114 (80.9)	
Indigenous African	76 (8.2)	32 (5.9)		21 (5.3)	11 (7.8)	
Asian Indian	69 (7.5)	45 (8.3)		34 (8.5)	11 (7.8)	
Mixed race	30 (3.2)	18 (3.3)		13 (3.3)	5 (3.5)	
HbA _{1c} % median (IQ)	8.3 (7.1-9.7)	8.5 (7.6-9.9)	0.001	8.4(7.5-9.8)	8.7 (7.8-10.2)	0.001
Total Cholesterol	5.0 (1.1)	5.3 (1.1)	0.001	5.2 (1.0)	5.7 (1.3)	<0.001
ACR	0.7 (0.4-1.4)	1.2 (0.6-3.8)	<0.001	1.02 (0.5-3.0)	2.6 (0.75-10.1)	<0.001
Smoker n (%)	163 (17.6)	124 (22.9)	0.013	92 (23.1)	32 (22.5)	0.045
Hypertensive n (%)	112 (12.1)	136 (25.1)	<0.001	85 (21.3)	51 (35.9)	<0.001
ACE n (%)	98 (10.6)	116 (21.4)	<0.001	70 (17.5)	46 (32.4)	<0.001
Aspirin n (%)	16 (1.7)	20 (3.7)	0.019	12* (3.0)	8 (11.6)	0.014

ACR - albumin creatinine ratio; ACE - angiotensin converting enzyme; yrs - years; n - numbers; SD - standard deviation; IQ - interquartile range

Table 5.4.11: Univariate logistic regression analysis for the presence of any DR, BDR and RDR in persons with T1DM

	Any DR OR (95% CI) n=541	BDR OR (95%CI) n=399	RDR OR (95% CI) n=142
Age at diagnosis: yrs			
< 14 (n=519)	1.00	1.00	1.00
14-26 (n=515)	1.01 (0.78, 1.30)	1.06 (0.80, 1.40)	0.86 (0.56, 1.32)
>26 (n=540)	0.57 (0.44, 0.74)	0.56 (0.42, 0.75)	0.59 (0.38, 0.90)
Male (n=846)	1.11 (0.90, 1.38)	1.11 (0.88, 1.41)	1.12 (0.78, 1.60)
Ethnicity:			
Caucasian (n=1,247)	1.00	1.00	1.00
Indigenous African (n=117)	0.71 (0.46, 1.09)	0.63 (0.38, 1.03)	0.95 (0.49, 1.84)
Asian Indian (n=118)	1.10 (0.74, 1.63)	1.12 (0.73, 1.72)	1.05 (0.54, 2.04)
Mixed Race (n=49)	1.01 (0.56, 1.84)	0.98 (0.51, 1.91)	1.10 (0.42, 2.88)
Duration of diabetes: yrs			
<7 (n=505)	1.00	1.00	1.00
7-15 (n=515)	8.89 (6.01, 13.15)	7.92 (5.21, 12.01)	16.19 (5.75, 45.60)
>15 (n=517)	26.20 (17.62, 38.95)	20.53 (13.46, 31.30)	68.74 (24.89, 189.88)
HbA _{1c} : %			
<7.0 (n=310)	1.00	1.00	1.00
7.0-7.9 (n=342)	1.78 (1.26, 2.52)	2.05, (1.39, 3.02)	1.15 (0.62, 2.12)
8.0-8.9 (n=322)	2.15 (1.52, 3.04)	2.30 (1.56, 3.39)	1.79 (1.01, 3.19)
≥9.0 (n=563)	2.05 (1.50, 2.81)	2.05 (1.43, 2.93)	2.06 (1.23, 3.44)
Total Cholesterol >5mmol/l (n=417)	1.72 (1.36, 2.18)	1.57 (1.21, 2.04)	2.19 (1.51, 3.18)
ACR >3mg/mmol (n=131)	2.91 (1.99, 4.25)	2.51 (1.65, 3.82)	4.11 (2.45, 6.87)
ACE inhibitors (n=253)	2.31 (1.72, 3.10)	1.80 (1.29, 2.51)	4.05 (2.69, 6.10)
Aspirin (n=44)	2.19 (1.12, 4.26)	1.77 (0.83, 3.77)	3.40 (1.43, 8.10)
Smokers (n=302)	1.39 (1.07, 1.81)	1.41 (1.05, 1.87)	1.36 (0.89, 2.09)
Hypertension (n=287)	2.44 (1.85, 3.22)	1.97 (1.44, 2.69)	4.08 (2.75, 6.06)

ACR - albumin creatinine ratio; ACE - angiotensin converting enzyme; yrs - years; n - numbers; OR - odds ration; 95% CI - 95% confidence interval

Table 5.4.12: Multivariate logistic regression analysis for the presence of any DR and referable DR in persons with T1DM

	Any DR OR (95% CI) n=541	BDR OR (95% CI) n = 399	RDR OR (95% CI) n=142
Age at diagnosis: yrs			
< 14 (n=519)	1.00	1.00	1.00
14-26 (n=515)	1.05 (0.77, 1.44)	1.12 (0.80, 1.55)	0.71 (0.42, 1.19)
>26 (n=540)	0.75 (0.54, 1.04)	0.76 (0.54, 1.09)	0.68 (0.39, 1.16)
Male: (n=846)	1.19 (0.92, 1.54)	1.16 (0.88, 1.52)	1.44 (0.94, 2.21)
Ethnicity:			
Caucasian (n=1,247)	1.00	1.00	1.00
Indigenous African (n=117)	1.75 (1.02, 3.04)	1.48 (0.81, 2.70)	3.38 (1.39, 8.22)
Asian Indian (n=118)	2.01 (1.23, 3.28)	1.93 (1.15, 3.23)	2.11 (0.92, 4.84)
Mixed Race (n=49)	1.29 (0.61, 2.70)	1.17 (0.53, 2.60)	1.06 (0.36, 3.17)
Duration of diabetes: yrs			
<7 (n=505)	1.00	1.00	1.00
7-15 (n=515)	10.35 (6.81, 15.75)	9.19 (5.90, 14.30)	20.80 (7.05, 61.37)
>15 (n=517)	37.64 (23.85, 59.40)	29.04 (17.95, 46.98)	127.61 (41.71, 390.41)
HbA _{1c} : %			
<7.0 (n=310)	1.00	1.00	1.00
7.0-7.9 (n=342)	1.33 (0.89, 1.99)	1.47 (0.96, 2.28)	0.94 (0.47, 1.88)
8.0-8.9 (n=322)	2.17 (1.44, 3.27)	2.25 (1.44, 3.51)	2.03 (1.03, 3.97)
>=9.0 (n=563)	3.26 (2.21, 4.81)	3.07 (2.01, 4.70)	4.14 (2.22, 7.39)
Smoker (n=302)	1.75 (1.26, 2.43)	1.72 (1.21, 2.43)	2.17 (1.27, 3.70)
Hypertensive (n=287)	1.45 (1.03, 2.04)	1.19 (0.81, 1.73)	2.30 (1.40, 3.75)

ACR - albumin creatinine ratio; ACE - angiotensin converting enzyme; yrs - years; n - numbers; OR - odds ratio; 95% CI - 95% confidence interval

Duration of diabetes

The prevalence of any DR, BDR and RDR increased with increasing duration of diabetes (Figure 5.4.8). In newly diagnosed persons with a duration of diabetes of ≤2 years the prevalence of any DR and RDR was 3.0% and 0.5% respectively (Table 5.4.13). In those with a duration of diabetes of 9-10 years this had increased to 34.1% with any DR and to 3.1% with RDR. Once duration of diabetes reached

19-20 years the prevalence of any DR, and RDR had increased to 73.6% and 25.0% respectively. When compared to those without DR those presenting with any DR, BDR or RDR had a significantly increased duration of diabetes (Table 5.4.10, page 202).

Figure 5.4.8: Prevalence of diabetic retinopathy by duration of T1DM

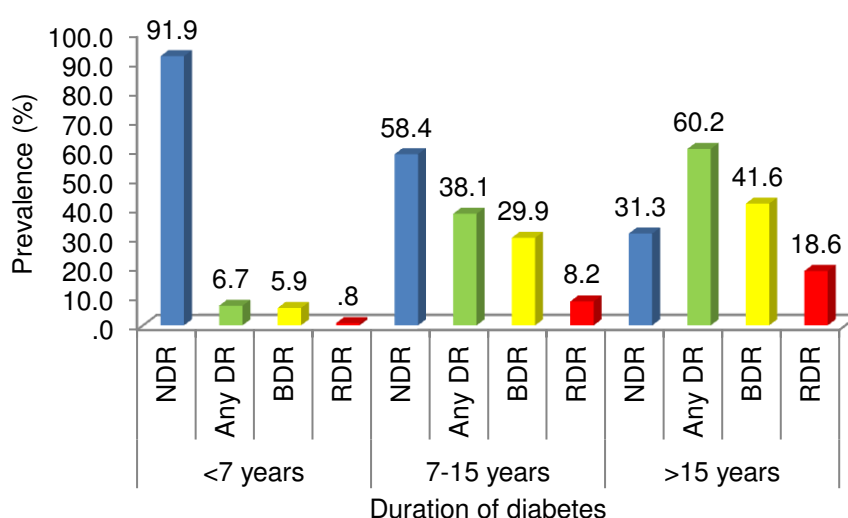


Table 5.4.13: The prevalence of any DR, BDR and RDR by duration of T1DM

Duration of diabetes (yrs)	n	Any DR % (95% CI)	BDR % (95% CI)	RDR % (95% CI)
0-2	203	3.0 (1.4, 6.3)	2.5 (1.1, 5.6)	0.49 (0.1, 2.7)
3-4	124	7.3 (3.9, 13.2)	5.7 (2.8, 11.2)	1.6 (0.4, 6.0)
5-6	171	11.1 (7.2, 16.7)	10.5 (6.8, 16.0)	0.58 (0.1, 3.2)
7-8	125	16.0 (10.6, 23.4)	12.8 (8.0, 19.8)	3.2 (1.3, 7.9)
9-10	129	34.1 (26.5, 42.6)	31.0 (23.7, 39.4)	3.1 (1.2, 7.7)
11-12	90	47.8 (37.8, 58.0)	38.9 (29.5, 49.2)	8.9 (4.6, 16.6)
13-14	96	57.3 (47.3, 66.7)	37.5 (28.5, 47.5)	19.8 (13.1, 28.9)
15-16	100	61.0 (51.2, 70.0)	46.0 (36.6, 55.7)	15.0 (9.3, 23.3)
17-18	74	70.3 (59.1, 79.5)	44.6 (33.8, 55.9)	25.7 (17.1, 36.7)
19-20	72	73.6 (62.4, 82.4)	48.6 (37.4, 59.9)	25.0 (16.4, 36.1)
21-22	64	67.2 (55.0, 77.4)	45.3 (33.7, 57.4)	21.9 (13.5, 33.4)
23-24	40	57.5 (42.2, 71.5)	55.0 (39.8, 69.3)	2.5 (4.4, 12.9)
25-28	57	70.2 (57.3, 80.5)	42.1 (30.2, 55.0)	28.1 (18.1, 40.8)
29+	123	59.4 (50.5, 67.6)	43.1 (34.7, 51.9)	16.3 (10.8, 23.8)

n - number; Any DR - any diabetic retinopathy; BDR - background diabetic; RDR - referable diabetic retinopathy; yrs - years

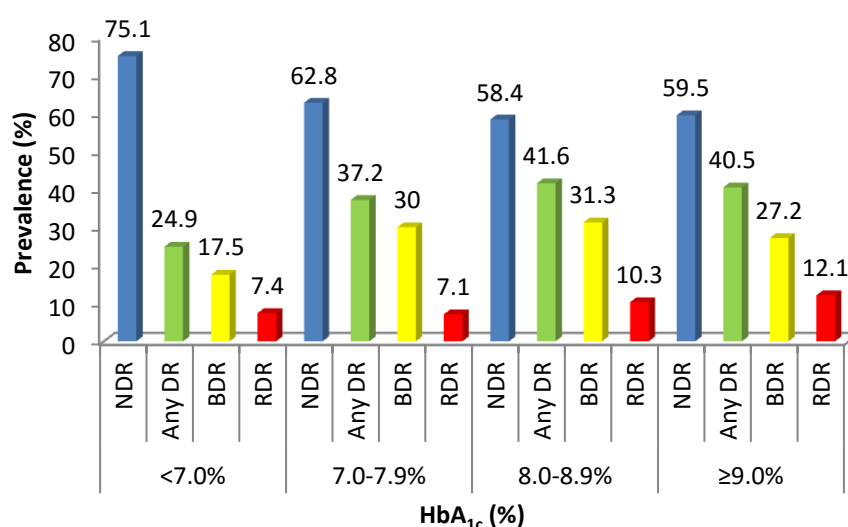
The findings in this population when subjected to univariate logistic regression analysis demonstrated that increasing duration of diabetes was the strongest risk factor for the presence of any DR (Table 5.4.11, page 203). Those with a duration of diabetes of 7-15 years had an 8.9-fold increased risk of having any DR, 7.9-fold of having BDR, and 16.2-fold of having RDR compared to those who had diabetes for <7 years. As the duration of diabetes increased to >15 years so did the risk of developing any DR, BDR and RDR increasing to a 26.2-, 20.5- and 68.7-fold risk respectively. After adjusting for age at diagnosis, gender, ethnicity, HbA_{1c}, smoking and hypertension increasing duration of diabetes remained the strongest risk factor for the presence of any DR, BDR and RDR (Table 5.4.12, page 204). Those with a duration of diabetes of 7-15 years had a 10.4-fold increased risk of having any DR, 9.2-fold of having BDR and 20-fold of developing RDR compared to those with diabetes for <7 years. When the duration of diabetes increased to >15 years the risk of having any DR, BDR and RDR increased to 37.6-, 29.0- and 127.6-fold.

Glycaemic control

The prevalence of any DR, BDR and RDR increased with increasing HbA_{1c} at the time of first screening (Figure 5.4.9). Those with any DR, BDR or RDR when compared to those without DR had a significantly higher HbA_{1c} level (Table 5.4.10, page 202). Increasing HbA_{1c} level increased the risk of presenting with any DR, BDR and RDR. In univariate analysis those with HbA_{1c} levels ≥9.0% had a 2.1-fold increased risk of presenting with any DR, BDR and RDR compared to those with a HbA_{1c} <7.0% (Table 5.4.11, page 203). After adjusting for age at diagnosis, gender, ethnicity, duration of diabetes, smoking and hypertension those with a HbA_{1c} of 7.0-7.9% had a 1.3- and 1.5-fold increased risk of having any DR and BDR respectively compared to those with a HbA_{1c} <7.0% (Table 5.4.12, page 204). However, there

was no significant increased risk of having RDR between those with a HbA_{1c} of 7.0-7.9% and <7.0%. As the HbA_{1c} level increased to 8.0-8.9% the risk of having any DR, BDR and RDR increased to 2.2-, 2.3- and 2.0-fold respectively compared to those with a HbA_{1c} of <7.0%. Once the HbA_{1c} was ≥9.0% the risk of having any DR, BDR or RDR increased to 3.3-, 3.1- and 4.1-fold respectively compared to those with a HbA_{1c} of <7.0%.

Figure 5.4.9: Prevalence of diabetic retinopathy by glycaemic control in persons with T1DM



Other risk factors

The risk factors significantly associated with the presence of any DR in univariate regression analysis were a high ACR, presence of hypertension, the use of ACE inhibitors, aspirin therapy, the habit of smoking, and total cholesterol levels (Table 5.4.11, page 203). The same significant associations were seen for the presence of BDR and RDR with the exception of the use of aspirin therapy for BDR and smoking for RDR. Although there was a significant association between ACR and any DR, BDR and RDR these data were not included in the subsequent stepwise multivariate analyses as data was missing for many of the persons screened. In multivariate analysis, risk factors independently associated with any DR were the

presence of hypertension and the habit of smoking, both of which increased the risk of any DR (Table 5.4.12, page 204). The presence of hypertension and smoking also significantly increased the risk of any DR and RDR, with the exception of hypertension which was no longer significant for the presence of BDR.

5.4.1.2.3 Summary of main findings

In the study population with T1DM:

- The prevalence of any DR was 36.9%, BDR 27.2% and RDR was 9.7%
- After having diabetes for ≥ 20 years, 73.6% had evidence of any DR and 25.0% had RDR
- At HbA_{1c} of $\leq 7.0\%$, 24.8% had any DR increasing to 40.6% with a HbA_{1c} of $\geq 9.0\%$, whilst for RDR the prevalence increased from 7.3% to 12.2% for the same HbA_{1c} levels respectively
- Increasing duration of diabetes and baseline HbA_{1c} levels were the strongest risk factors for the presence of any DR, BDR and RDR after adjusting for confounders
- Other risk factors independently associated with any DR, BDR and RDR were ethnicity with Asian Indian's at higher risk of any DR and BDR and Indigenous Africans at a higher risk of RDR, compared to Caucasians after adjusting for confounders.
- Those with hypertension and those who smoked were also at an increased risk of any DR, BDR and RDR after adjusting for confounders.

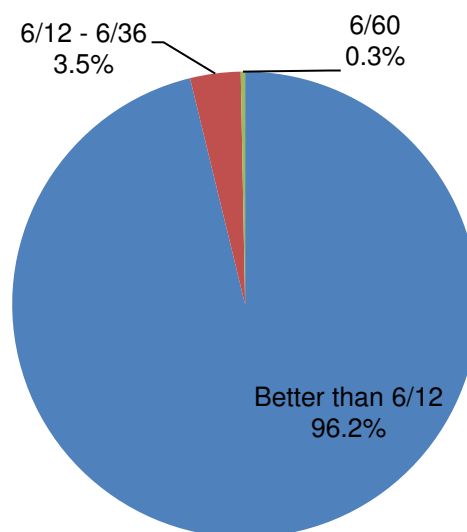
5.4.2 Visual acuity

5.4.2.1 T2DM

5.4.2.1.1 Prevalence of visual impairment and blindness

There were 74.1% (2,946) with a recorded visual acuity at the time of screening. Reasons for not recording visual acuity were not provided. The majority (96.2%) of those who had visual acuity testing, had normal vision at first screening (Figure 5.4.10), 3.5% had visual impairment (6/12-6/36) and 0.3% were blind (6/60 or worse) in their better seeing eye.

Figure 5.4.10: Prevalence of normal vision, visual impairment and blindness in persons with T2DM at first screening

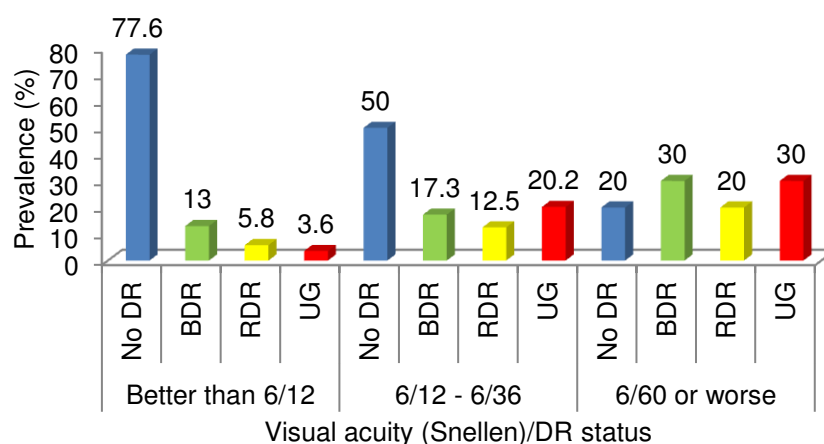


The prevalence of DR and ungradeable images (due to media opacification) increased in line with worsening visual acuity. The prevalence of RDR increased from 5.8% in those with normal vision to 12.5% in those with visual impairment, and 20% in those who were blind. The prevalence of ungradeable images increased

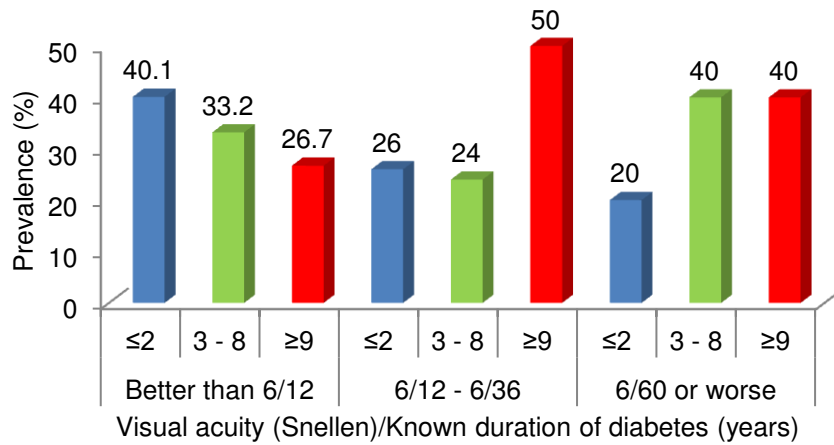
from 3.6% in those with normal vision to 20.2% in those with visual impairment, and 30% in those who were blind (Figure 5.4.11a). The proportion of persons with relatively newly diagnosed T2DM (≤ 2 years) decreased as visual acuity worsened. Of those persons with normal vision, 40.1% had had diabetes for <3 years with the proportion decreasing to 26% for those with visual impairment, and down to 20% for those who were blind (Figure 5.4.11b). Even though the proportion of persons with visual impairment (50%) was highest in those with T2DM for ≥ 9 years, the proportion of persons who were blind (40%) had had T2DM for 3-8 years. The proportion of persons aged ≥ 63 years with normal vision increased from 27.7%, to 69.2% with visual impairment and 70% in persons who were blind (Figure 5.4.11c).

Figure 5.4.11: Prevalence of normal vision, visual impairment and blindness with a) DR status, b) duration of diabetes c) age, in persons with T2DM

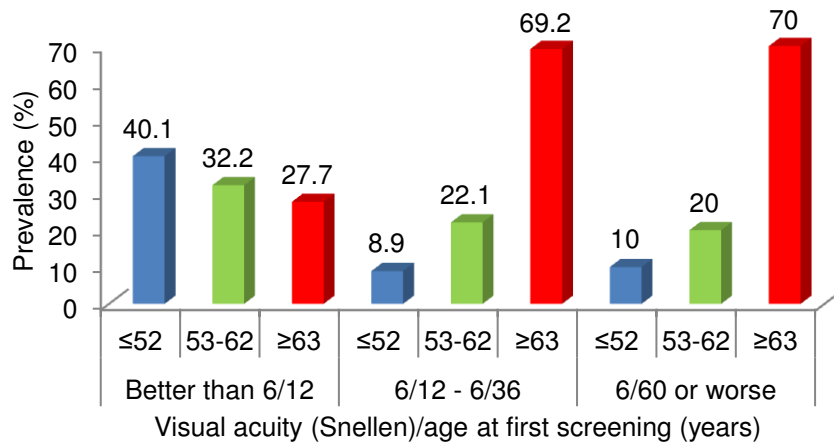
a)



b)



c)

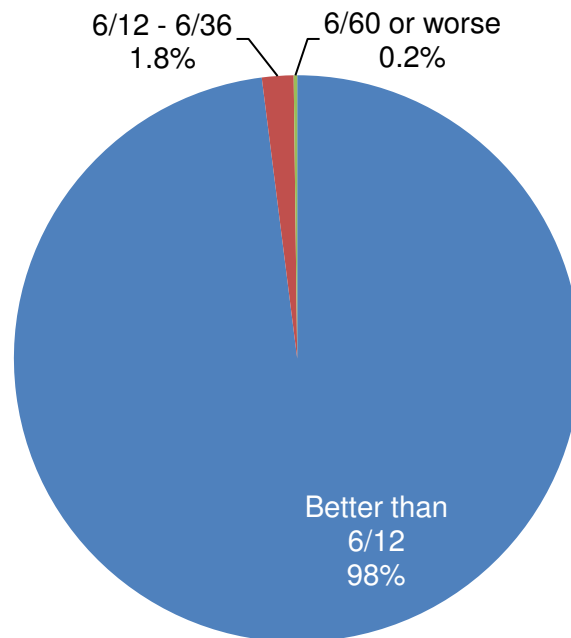


5.4.2.2 T1DM

5.4.2.2.1 Prevalence of visual impairment and blindness

Only 57.8% (889) of persons with T1DM had a recorded visual acuity at the time of screening. Reasons for not recording visual acuity were not recorded. Almost all of those tested (98.0%, n = 889) had a visual acuity of better than 6/12 (normal vision) in their better seeing eye (Figure 5.4.7), 1.8% (16) had a visual acuity of 6/12-6/36 (visual impairment) and 0.2% (2) had a visual acuity of 6/60 or worse (blind) (Figure 5.4.12).

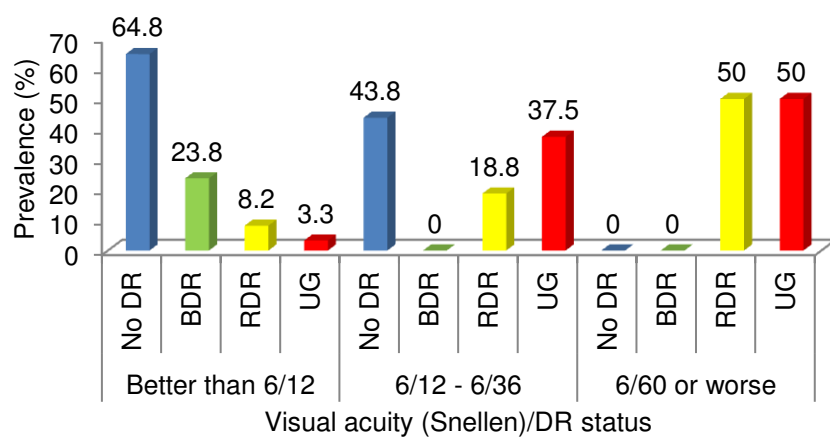
Figure 5.4.12: Visual acuity in persons with T1DM at first screening



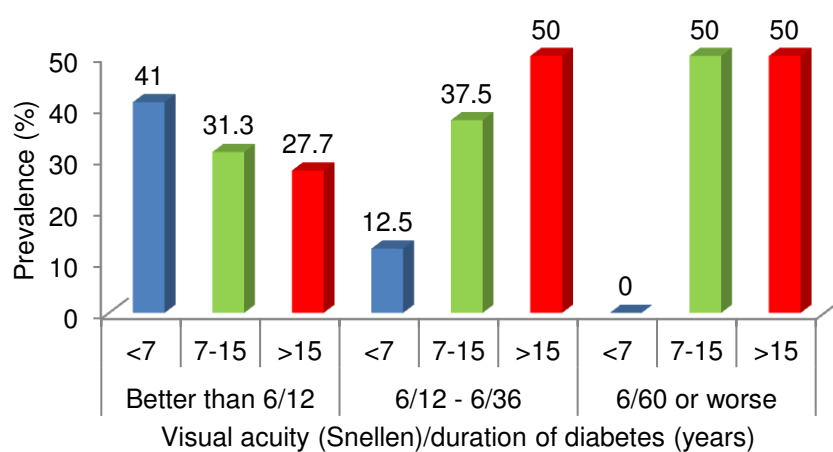
There was a slight increase in the prevalence of visual impairment and blindness in those who had RDR at first screening compared to those without DR (Figure 5.4.13a). As duration of diabetes increased the prevalence of normal vision decreased and visual impairment increased, whilst the prevalence of blindness remained unchanged (Figure 5.4.13b). However, the largest increase in the prevalence of visual impairment and blindness occurred in those subjects whose images were ungradeable. The prevalence of normal vision decreased slightly with increasing age (Figure 5.4.13c).

Figure 5.4.13: Prevalence of normal vision, visual impairment and blindness with a) DR status, b) duration of diabetes and c) age in persons with T1DM

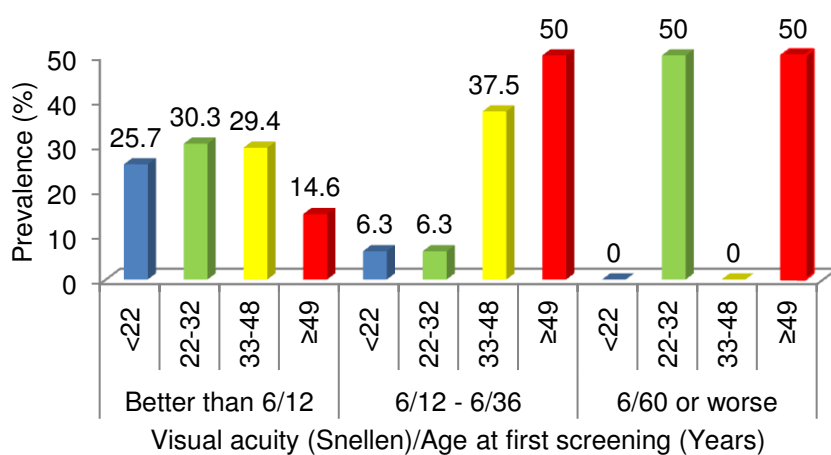
a)



b)



c)



5.4.2.3 Summary of main findings

- The prevalence of visual impairment and blindness was low in persons with T2DM at 3.5% and 0.3% respectively, and was low in those with T1DM at 1.8% and 0.2% respectively.
- The prevalence of visual impairment and blindness was higher in persons with RDR compared to those without DR and highest in those with ungradeable images in persons with either T2DM or T1DM.

5.5 Discussion

Within this special but limited sub-study of a cohort of persons with T2DM and T1DM undergoing retinal photography within a private diabetes management programme in South Africa, at the time of their first screening visit the prevalence of any DR was 20.5%, BDR was 14.1% and RDR was 6.4% in T2DM, and 36.9%, 27.2% and 9.7% respectively in T1DM. Two other studies, (Mash et al. 2007, Read et al. 2007) have previously reported the prevalence of DR in people with diabetes attending community clinics in Cape Town, South Africa. Mash et al evaluated the implementation of a pilot screening service utilising a mobile screening NM digital camera in primary care. In 400 patients screened the prevalence of any DR was 63% (combined T2DM and T1DM), and RDR 43%. (Mash et al. 2007) Read et al evaluated the level of DR in 248 consecutive persons with T2DM attending a primary care clinic, the prevalence of DR was 32.3% and 8.9% had RDR. (Read et al. 2007) However the assessment of DR was by undilated direct ophthalmoscope with dilation used only if DR lesions were seen. As the sensitivity and specificity of direct ophthalmoscopy is inferior to retinal photography this may be a reason for the difference in prevalence of DR reported. (Harding et al. 1995) In a further study

using a 60° mydriatic fundus camera the prevalence of any DR was 33.4% as assessed by endocrinologists, and 26.5% when assessed by ophthalmologists with severe DR at 11.7%, and 12.6% respectively.(Joannou et al. 1996) In a third and similar study comparing 60° colour photography versus clinicians' fundus examinations the prevalence of any DR was 30.6%, with severe DR in 12.3% as determined by the reference standard.(Carmichael et al. 2005) Therefore, the prevalence of DR in persons with T2DM reported in this study of patients attending a private clinic was lower than previously seen from community based studies in South Africa. This may be due to the differences in the ethnicity and socio-demographics of the populations accessing private and public health care services in South Africa. In comparison to this study, where the majority were Caucasian's (71%), Read et al had a majority of Indigenous African (50%) with only 2% Caucasian, (Read et al. 2007) Levitt et al had all Indigenous Africans, (Levitt et al. 1997) Carmichael et al had 49% Caucasians, 39% Indigenous Africans, (Carmichael et al. 2005) whilst Joannou et al had a population of 30% Indigenous African/Indian.(Joannou et al. 1996)

Ethnic differences in the prevalence of any DR have previously been reported to be higher in non-Caucasian persons when compared to Caucasians or Europeans, (West et al. 1982, Stolk et al. 2008, Raymond et al. 2009) and similarly for severe/referable stages of DR.(Ross et al. 2007, Stolk et al. 2008) Only two previous studies of persons with diabetes, with relative small numbers of patients, have examined differences between ethnic groups in South Africa.(Kalk et al. 1997, Read et al. 2007) One study did not report any significant associations between ethnicity (Indigenous Africans, Mixed Race and Caucasians) and DR(Read et al. 2007); whilst another study found that those of an African and Indian origin had a

significantly higher prevalence of severe DR than Caucasians.(Kalk et al. 1997)

However a small sample size (248 patients) and method of DR detection being direct ophthalmoscopy may have limited the findings by Read et al.(Read et al. 2007) In contrast, we observed clear differences in the risk of DR between the ethnic groups we studied in the cohort of subjects attending the CDE in Johannesburg during 2001 to 2010. Whilst the risk of any DR was increased in Asian Indians, RDR was higher in Indigenous Africans with T1DM when compared to Caucasians. The risk of both any DR and RDR was increased for all non-Caucasian populations, with those of Mixed Race at the greatest risk compared to Caucasians with T2DM. These differences seen between Caucasians and non-Caucasians remained after correction for other risk factors, including HbA_{1c} at baseline and age at diagnosis of diabetes. Possible explanations include differences in tissue response to chronic glycaemia due to ethnicity, as well as unrelated factors, such as erythrocyte turnover or the rate of protein glycation, presence of anaemia (especially haemolytic anaemia, thalassaemia and sickle cell anaemia).(Hare et al. 2012) There is also some evidence that HbA_{1c} may vary independently of glycaemia among people of different ethnicities.(Ziemer et al. 2010, Chapp-Jumbo et al. 2012, Hare et al. 2012) Those of black origin were found to have higher HbA_{1c} levels than Caucasians after adjusting for confounders in persons without diabetes, impaired glucose tolerance and with known diabetes. Previous studies have also found associations between polymorphisms of specific genes, for example the endothelial nitric oxide synthase gene, and DR in different ethnicities, including African populations.(Chen et al. 2007) Therefore, whether the increased risk in prevalence of RDR in non-Caucasians is due to differences in the presence and/or response to putative risk factors or some unknown gene or genes are still unclear.(Burgess et al. 2013)

In our cohort Increasing duration of diabetes was the most significant risk factor associated with the presence of any DR, BDR and RDR in both T2DM and T1DM, which has also been consistently shown in almost all studies of prevalence,(Klein et al. 1984a, b, Kristinsson et al. 1994a, Kristinsson et al. 1994b, Henricsson et al. 1996, Dowse et al. 1998, Younis et al. 2002, Misra et al. 2009, American Diabetes Association 2010b, Zhang et al. 2010, Yau et al. 2012) including the DRSSW population reported in Chapter 3.(Thomas et al. 2014)

In both persons with T2DM and T1DM the risk of any DR, BDR and RDR increased with increasing HbA_{1c} at time of initial screening. Those with T1DM with an HbA_{1c} above 8.0% had a 2 to 4 fold increased odds of having any DR, BDR and RDR compared to those with a HbA_{1c} of 7.0% or less. There was no significant difference comparing T1DM subjects with an HbA_{1c} between 7.0% and 7.9% and those with a HbA_{1c} of less than 7.0%. In T2DM there was an increased risk of any DR, BDR and RDR associated with each incremental quartile of HbA_{1c} compared to those with a HbA_{1c} of 6.5% or less. Previous clinical trials (The Diabetes Control and Complications Trial Research Group 1993, 1995, UK Prospective diabetes study group 1998a, The ADVANCE Collaborative Group. 2008, Duckworth et al. 2009) have reported that for every 1% decrease in HbA_{1c} the risk of DR is reduced by 37%, with the progression to sight-threatening DR reduced by 25%, the need for laser therapy by 25% and blindness by 15%.(Cheung et al. 2010) The effect of early intensive therapy to achieve good glycaemic control appears to be long lasting and referred to as 'metabolic memory'.(White et al. 2008) However, a glycaemic threshold below which no apparent benefits in risk reduction is controversial, with a meta-analysis finding reductions in the frequency of DR below the diagnostic criteria for diabetes.(Wong et al. 2008) However, clinical trials have not found any

additional benefit in aggressive glycaemic control, $\text{HbA}_{1c} < 6.5\%$, on the development or progression of DR, (Gerstein et al. 2008, The ADVANCE Collaborative Group. 2008) with further findings suggesting a possible increase in mortality at the lower HbA_{1c} range due to hypoglycaemia. (Liew et al. 2009) Therefore, the increased risk of hypoglycaemia with aggressive glycaemic targets should also be kept in mind in arriving at the best efficacy: adverse effect balance for each individual person.

Hypertension was shown to be a significant risk factor for DR only in persons with T1DM. Previous epidemiological studies and clinical trials have shown hypertension as an important modifiable risk factor for DR, (Mohamed et al. 2007, Gallego et al. 2008, Klein et al. 2008) but not in all studies. (ACCORD study group et al. 2010) The UKPDS (UK Prospective diabetes study group 1998b, Matthews et al. 2004) demonstrated that for every 10mmHg decrease in systolic blood pressure the risk of DR progression was reduced by 35%, the need for laser therapy by 35% and visual loss by 50%, (Cheung et al. 2010) but these benefits have not been sustainable without continued long-term maintenance of blood pressure control. (Holman et al. 2008) Some clinical trials (Chaturvedi et al. 1998, Chaturvedi et al. 2008, Mitchell et al. 2008, Sjolie et al. 2008, Mauer et al. 2009) investigating the effects of a RAS inhibitors have reported benefits for DR. The DIRECT study investigating the effects of Candesartan in T2DM and T1DM have found reductions in the risk and progression of DR in persons with T1DM, (Chaturvedi et al. 2008) and increased regression of DR in persons with T2DM, (Sjolie et al. 2008) independent of changes in blood pressure. However, the ADVANCE study did not show any beneficial effects of the combination of perindopril and indapamide on DR in persons with T2DM. (Patel et al. 2007) A reason for the lack of an effect for

persons with T2DM, in contrast to the UKPDS, (UK Prospective diabetes study group 1998b) may be due to the more aggressive treatment of hypertension and lower blood pressure targets in this patient group. In this study, the use of ACE inhibitors was associated with an increased risk of DR in both T2DM and T1DM. However, the use of aspirin therapy was only associated with an increased risk of any DR and RDR in T1DM, and not at all in T2DM. Yet having adjusted for confounders, the use of ACE inhibitors and aspirin were no longer significant and were removed from the analysis. Previously, the ETDRS found that aspirin had no beneficial effects on the progression of DR in persons with mild to severe non-PDR or early PDR. (Early Treatment Diabetic Retinopathy Study Research Group 1991) However, in the early stages of DR aspirin has been shown to slow the progression of microaneurysms by more than 50% over 3 years. (The DAMAD Study Group 1989)

The relevance of smoking as a risk factor for DR is inconclusive and controversial, with some studies showing a positive association, (Anonymous 1977, Klein et al. 1983, UKPDS group 1990, Kohner et al. 1998) with others showing no association, (Klein et al. 1983, Kohner et al. 1998) whilst others suggest that smoking may be protective against the development of DR. (Stratton et al. 2001) Interestingly in our study, smoking was also inconclusive as a risk factor, with associations shown only for the development of RDR and only in persons with T1DM after adjusting for confounders.

In our study population there was a low level of visual impairment and blindness in both T2DM and T1DM. The prevalence of visual impairment was higher in persons

with T2DM compared to that of T1DM at 3.5% versus 1.8% respectively, although the prevalence of blindness was similar in both at 0.3% and 0.2% respectively. This difference may be explained by the older age of the T2DM population. Two studies have reported the prevalence of visual impairment in the African region at 8.5% and severely visually impaired or blindness at 3.6% (Glover et al. 2012) and 28.8% and 11.4% respectively. (Mash et al. 2007) however, these studies did not report visual acuity separately for T2DM and T1DM. Even so the prevalence of visual impairment and blindness in the CDE cohort were much lower than that previously reported, which may again be accounted for by differences in the population characteristics and socioeconomic status and/or genetic makeup.

As DR is one of the major causes of blindness and visual impairment in people with diabetes, it is reasonable to assume that risk factors for DR would also be associated with visual impairment and blindness. (Deckert et al. 1967, Nielsen 1984a, b, Rand et al. 1985, Agardh et al. 1993, Reichard 1995) In the CDE cohort, the prevalence of visual impairment and blindness was highest in those with ungradeable images. The most common cause of ungradeable images in screening programmes is cataract, media opacity and poor pupil dilation. (Thomas et al. 2014) Information on other eye conditions found during the screening process was not available for analysis in this study, and so could not be investigated further.

Compared to previous population based studies in Africa and South Africa the strength of this study was the relatively larger sample size, although still small in epidemiological terms, and that all the data (i.e. retinal images and the putative risk factors) were collected at a single centre utilising standard protocols. However, as most of the diabetes population in South Africa utilise the public health system and are of Indigenous African descent, the population studied here utilising the private

health system and being predominantly Caucasian is therefore not representative of the majority of persons with diabetes in South Africa. Whilst the use of standardised digital retinal photography and grading protocol are strengths within this study, the lack of dilation may have led to a higher proportion of ungradeable images and the availability of only one 45° fields per eye may have resulted in under reporting of DR.

5.5.1 Summary of main findings

- In this population of persons with diabetes entering a private diabetes management programme in Johannesburg, SA, there was a low prevalence of DR.
- Ethnicity was independently associated with the presence of DR and RDR at the time of first screening in both T2DM and T1DM.
- Increasing duration of diabetes and poor glycaemic control were the strongest risk factors associated any DR and RDR in persons in both T2DM and T1DM.
- In T1DM hypertension and smoking were additional risk factors for the presence of any DR and RDR.

Chapter 6

Incidence of diabetic retinopathy and assessment of
screening intervals in a private healthcare setting in the
Centre for Diabetes and Endocrinology (CDE)
Johannesburg, South Africa

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6.1 Introduction

The incidence of DR within South Africa, has not previously been adequately reported. It has been estimated that diabetes, because of DR and cataracts accounts for 8,000 new cases of vision impairment every year.(Hofman et al. 2014)

Previous studies in Europe have assessed the risk of developing DR, for the purpose of defining the most appropriate screening interval for individual patients, based on a minimal number of risk factors for DR available for analysis i.e. age, gender, duration of diabetes, type of diabetes and treatment for diabetes.(Younis et al. 2003a, Younis et al. 2003b, Olafsdottir et al. 2007, Agardh et al. 2011, Jones et al. 2012, Thomas et al. 2012) The availability of additional putative risk factors including glycaemic control, blood pressure and cholesterol should make it possible to better individualise the screening interval. There is also additional evidence which suggests that the risk of DR could vary with ethnicity.(West et al. 1982, Ross et al. 2007, Stolk et al. 2008, Raymond et al. 2009) Therefore, the CDE dataset which was provided afforded me an unique opportunity to assess appropriate screening intervals with these additional putative risk factors available, although relatively small in numbers.

6.2 Aims

The primary aim of this chapter was to determine:

- whether an annual screening interval is necessary in all persons with diabetes without any evidence of DR at initial screening based on a single 45 degree central field (posterior pole) digital image acquired without mydriasis

In order to determine the appropriate screening intervals the secondary aims of this chapter were to determine:

- the seven year cumulative incidence of any DR, BDR and RDR in persons with T2DM and T1DM in the stated population in Johannesburg, South Africa
- the risk factors associated with the incidence of any DR, BDR and RDR in both T2DM and T1DM over the study period

6.3 Methods

At entry into the disease management programme retinal photographs are taken alongside measures of HbA_{1c}, ACR and total cholesterol as well as recording the presence and/or treatment for hypertension and the habit of smoking (see Methods Chapter 2). These assessments are then repeated on at least an annual basis if not more frequently. The study population was followed up over a period of seven years from 2001-2010.

To allow analysis of ethnic origin, due to the relatively small population sizes of both T2DM and T1DM ethnicity was grouped as Caucasian and non-Caucasians which comprised of Indigenous Africans, Asian Indians and persons of Mixed Race.

Details of the statistical methods used in this chapter are described in Chapter 2. In addition to the basic descriptive analyses used throughout, survival analyses, Kaplan Meier and Cox proportional hazards methods were also employed to estimate the incidence of any DR, BDR and RDR, as well as to examine the putative risk factors collected and their association with the development and or progression of DR. Using the available risk factors associated with the incidence of RDR, incidence rates according to glycaemic control, duration of diabetes and

ethnicity were estimated to elucidate the impact of different screening intervals within this population.

The subsets investigated were:

for T2DM:

A) Glycaemic control and known duration of diabetes sub-grouped as follows:

- $\text{HbA}_{1c} \leq 7.0\%$ with a known duration of diabetes ≤ 10 years
- $\text{HbA}_{1c} \leq 7.0\%$ with a known duration of diabetes > 10 years
- $\text{HbA}_{1c} > 7.0\%$ with a known duration of diabetes ≤ 10 years
- $\text{HbA}_{1c} > 7.0\%$ with a known duration of diabetes > 10 years

and for T1DM:

A) Ethnicity and glycaemic control sub-grouped as follows

- Caucasians with an $\text{HbA}_{1c} \leq 7.0\%$
- Non-Caucasians with an $\text{HbA}_{1c} \leq 7.0\%$
- Caucasian with an $\text{HbA}_{1c} > 7.0\%$
- Non-Caucasians with an $\text{HbA}_{1c} > 7.0\%$

B) Ethnicity and duration of diabetes sub-grouped as follows:

- Caucasians with a duration of diabetes ≤ 10 years
- non-Caucasians with a duration of diabetes ≤ 10 years
- Caucasians with a duration of diabetes > 10 years
- non-Caucasians with a duration of diabetes > 10 years

C) Glycaemic control and duration of diabetes sub-grouped as follows:

- HbA_{1c} ≤7.0% with a duration of diabetes ≤10 years
- HbA_{1c} ≤7.0% with a duration of diabetes >10 years
- HbA_{1c} >7.0% with a duration of diabetes ≤10 years
- HbA_{1c} >7.0% with a duration of diabetes >10 years

6.4 Results

Of the 3,941 persons with diabetes without evidence of DR at initial screening, 60.2% (2,371) had at least 1 further screening event within the study period and were included in the following analysis. Reasons for not having a second screening event included: non-attendance, cancellation of medical aid, emigration or death. Due to the anonymisation of the data, this could not be investigated further.

6.4.1. T2DM

6.4.1.1 Incident DR in persons with T2DM

There were 2,968 persons with T2DM without DR at their first DR screening event at the CDE, Johannesburg, South Africa. 57.3% (1,702) underwent at least 1 further screening episode and 42.7% (1,266) did not. Of those who did not have any further screening within the time period of the study 22.6% (286) were deemed not eligible as a second screening event would have occurred before 12 months of the end of the study period. The remaining 77.2% (977) although eligible unfortunately did not receive and or attend for a further screening episode. Those who did have a second screening event were significantly older, with a lower HbA_{1c} level and contained a higher proportion of Caucasians (Table 6.4.1) compared to those who did not have a repeat screening event.

Of those included in the analysis, the majority were Caucasian with a mean age 56.8 years and a median known duration of diabetes of 4.0 years (Table 6.4.1). The majority (74.7%) were Caucasian, with only 10.9% Indigenous Africans, 11.3% Indian Asians and 2.7% of Mixed Race. The mean age at diagnosis of diabetes was 51.5 years and the median HbA_{1c} at first screening was 7.2%.

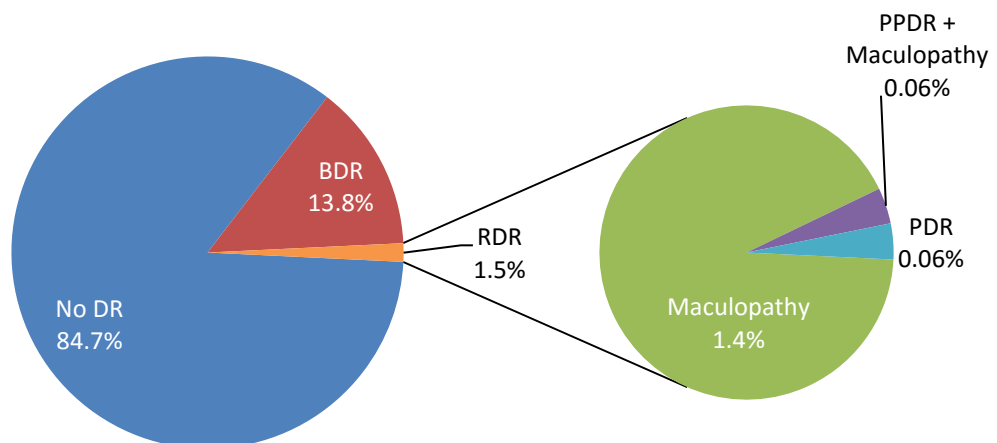
Tables 6.4.1: Baseline characteristics between persons with T2DM who attended for a second screening event and therefore included in the study and those who were eligible but did not.

	<i>No second screening (977)</i>	<i>Included (1,702)</i>	<i>P value</i>
Age years mean (SD)	55.5 (12.2)	56.8 (11.5)	0.008
Gender: n (%)			0.996
Male	652 (66.7)	1,136 (66.7)	
Female	325 (33.3)	566 (33.3)	
Ethnicity: n (%)			<0.001
Caucasian	648 (66.3)	1,271 (74.7)	
Indigenous African	143 (14.6)	186 (10.9)	
Indian Asian	142 (14.5)	192 (11.3)	
Mixed Race	40 (4.1)	46 (2.7)	
Known duration of diabetes years median (IQ)	3.0 (1.0-7.0)	4.0 (1.0-8.0)	0.082
Age at diagnosis years mean (SD)	50.6 (11.9)	51.5 (11.5)	0.050
HbA _{1c} % median (IQ)	7.6 (6.6-9.0)	7.2 (6.5-8.3)	<0.001
Total Cholesterol (mmol/l) mean (SD)	5.1 (1.3)	4.9 (1.1)	0.022
ACR median (IQ)	1.0 (0.52-3.0)	0.91 (0.48-2.5)	0.246
Other therapies: n (%)			
Aspirin	794 (81.3)	1,416 (83.2)	0.206
ACE	183 (18.7)	286 (16.8)	0.027
Hypertension n (%)	491 (50.3)	896 (52.6)	0.234
Smokers n (%)	185 (18.9)	229 (13.5)	<0.001

Key: ACR - Albumin:Creatinine ratio; ACE - Angiotensin Converting Enzyme inhibitors;

Of the 2,968 persons with T2DM without DR at first screening, 1,710 (57.6%) persons underwent a second screening event, 1,121(37.8%) underwent a third screening event, 734 (24.7%) a fourth, 440 (14.8%) a fifth , 231 (7.8%) a sixth, 96 (3.2%) a seventh, 28 (0.9%) an eighth and 2 (0.07%) a ninth screening event. The average screening intervals ranged from 1.0 (0.9) year between the first and second screening events to 0.6 (0.5) years between the seventh and eighth screening events. Over the study period, 15.3% (262) developed DR, of which, 13.8% (236) had BDR and 1.5% (26) RDR (Figure 6.4.1). The RDR group consisted of 1.4% (24) who developed maculopathy, 0.06% developed PPDR with maculopathy and 0.06% developed PDR alone without maculopathy. Only one person developed PDR, however images at their second screening event were ungradeable. Therefore, the PDR was only visible at the third screening event which was 2.8 years after the initial negative screen. This person was a 59 year old male, Caucasian with a 4 year history of diabetes at the first screening event and an HbA_{1c} of 7.1%. He was a non-smoker, did not have hypertension and was not receiving aspirin or an ACE inhibitor. At the third screening event when the PDR was seen the HbA_{1c} had only slightly worsened to 7.6%, hypertension had developed and he was being treated with ACE inhibitors and aspirin.

6.4.1: Incidence of DR during the 7 year study period in persons with T2DM



The overall incidence of any DR, BDR and RDR over the course of the seven year study period is shown in Table 6.4.2 and Figure 6.4.2. The annual incidence (cases per 1,000 persons) of any DR increased from 18 cases in the first year to 83 cases in the seventh year. The annual incidence of RDR increased from 1 case in the first year to 20 cases in the sixth year and an additional 10 cases in the seventh year. The seven year cumulative incidence of any DR, BDR and RDR was 351 (35.1%), 331 (33.1%) and 47 (4.7%) cases respectively.

Table 6.4.2: Annual and cumulative incidence of any DR, BDR and RDR in persons with T2DM

Time (yrs)	Number	<i>Any DR</i>	
		Annual incidence	Cum incidence (95% CI)
1	1,545	18.0	18.0 (17.98, 18.02)
2	1,132	59.0	77.0 (76.9, 77.1)
3	798	62.0	139.0 (138.7, 139.3)
4	543	39.0	178.0 (177.5, 178.5)
5	350	35.0	213.0 (212.1, 213.9)
6	182	55.0	268.0 (265.9, 270.1)
7	46	83.0	351.0 (341.3, 360.7)

Time (yrs)	Number	BDR	
		Annual incidence	Cum incidence (95% CI)
1	1,522	17.0	17.0 (16.98, 17.02)
2	1,119	56.0	69.0 (68.9, 69.1)
3	792	59.0	126.0 (125.7, 126.3)
4	541	40.0	160.0 (159.5, 160.5)
5	349	36.0	195.0 (194.1, 195.9)
6	181	54.0	251.0 (249.0, 253.0)
7	46	89.0	331.0 (321.6, 340.4)

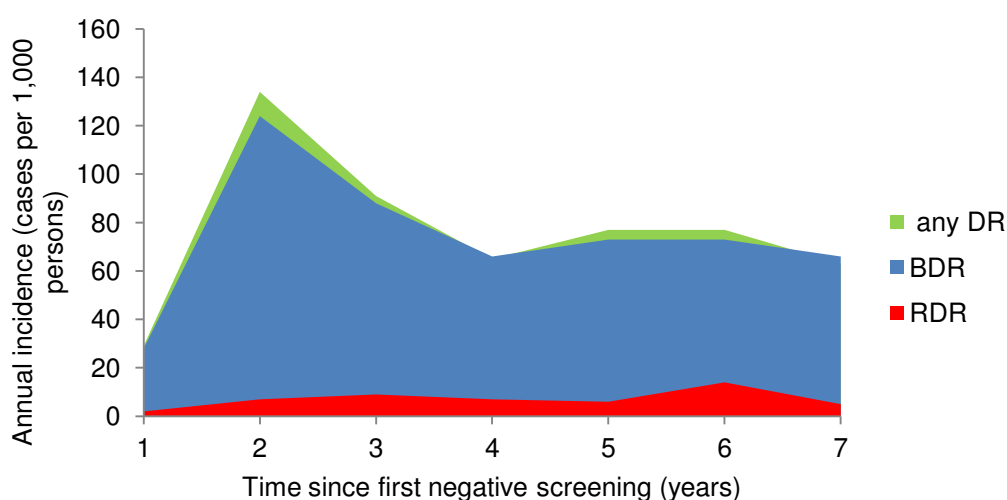
Table 6.4.2 continued

Time (yrs)	Number	<i>RDR</i>	
		Annual incidence	Cum incidence (95% CI)
1	1,561	1.0	1.0 (0.99, 1.0)
2	1,192	4.0	5.0 (4.99, 5.01)
3	876	6.0	11.0 (10.98, 11.02)
4	624	2.0	13.0 (12.96, 13.04)
5	421	5.0	17.0 (16.9, 17.1)
6	228	20.0	37.0 (36.7, 37.3)
7	61	10.0	47.0 (45.6, 48.4)

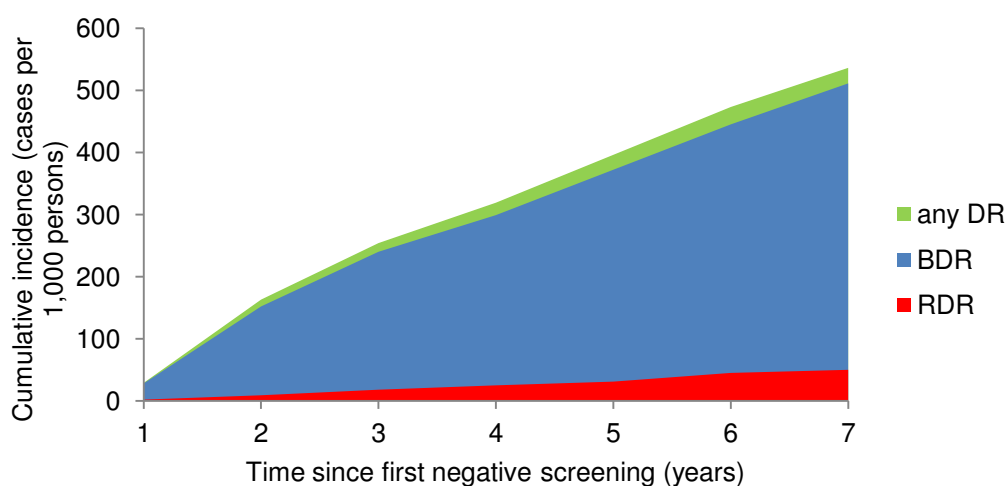
Number - Number remaining at risk; cum incidence - cumulative incidence; Any DR - any diabetic retinopathy; BDR background diabetic retinopathy; RDR - referable diabetic retinopathy; yrs - years; Incidence is number of cases per 1,000 persons

Figure 6.4.2: a) Annual and b) cumulative incidence of any DR, BDR and RDR in persons with T2DM

a)



b)



6.4.1.2 Risk factors for incident DR

The characteristics at first screening of those who developed any DR, BDR and RDR and those who remained free of DR over the course of the seven year study period are shown in table 6.4.3. There were no significant differences between those who developed any DR and those who remained free from DR for age, gender, total cholesterol, ACR, smoking status, hypertension and the use of ACE inhibitors. There were also no significant differences between the Kaplan Meier curves for gender, total cholesterol, ACR, smoking status and the use of aspirin. These risk factors were also not significant between those who developed BDR and RDR and those who remained free of DR with the exception of gender for the development of BDR, where females were at a decreased risk compared to males, and the use of ACE inhibitors which decreased the risk of development of RDR (Table 6.4.4, page 234).

Table 6.4.3: Characteristics at first screening for persons with T2DM who remained free of DR and those who developed any DR, BDR and RDR during the course of the study

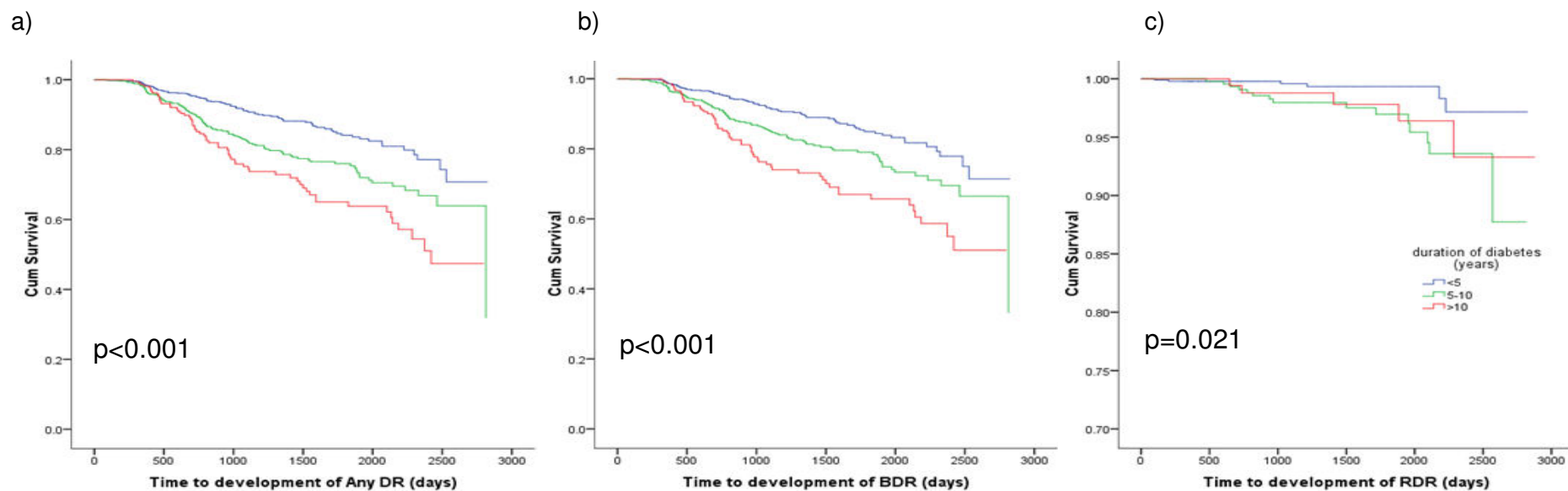
	<i>NDR</i> (1,448)	<i>Any DR</i> (262)	<i>p</i> <i>value</i>	<i>BDR</i> (236)	<i>p</i> <i>value</i>	<i>RDR</i> (26)	<i>p</i> <i>value</i>
Age years mean (SD)	56.9 (11.4)	56.3 (12.4)	0.472	56.5 (12.7)	0.689	54.1 (9.7)	0.233
Gender: n (%)			0.083		0.034		0.325
Male	954 (65.9)	187 (71.4)		172 (72.9)		15 (57.7)	
Female	494 (34.1)	75 (28.6)		64 (27.1)		11 (42.3)	
Known duration years mean (SD)	3.0 (1.0-7.0)	6.0 (3.0-10.0)	<0.001	6.0 (2.3-10.0)	<0.001	6.0 (4.8 – 10.0)	0.088
Age at diagnosis years mean (SD)	52.0 (11.4)	48.7 (12.0)	<0.001	48.9 (12.3)	<0.001	47.0 (9.0)	0.042
Ethnicity: n (%)			0.050		0.101		0.483
Caucasian	1,097 (76.0)	180 (68.7)		164 (69.8)		16 (64.0)	
Indigenous African	149 (10.3)	38 (14.5)		33 (14.0)		5 (20.0)	
Asian	162 (11.2)	31 (11.8)		28 (11.9)		3 (12.0)	
Mixed race	35 (2.4)	11 (4.2)		10 (4.3)		1 (4.0)	
HbA _{1c} % median (IQ)	7.1 (6.5-8.1)	8.0 (7.0-9.3)	<0.001	7.9 (7.0-9.2)	<0.001	8.7 (7.1-11.3)	0.002
Total Cholesterol (mmol/l) mean (SD)	4.9 (1.1)	4.9 (1.1)	0.791	4.9 (1.0)	0.508	5.3 (1.5)	0.250
ACR median (IQ)	0.88 (0.47-2.45)	1.1 (0.56-3.2)	0.191	1.1 (0.58-3.8)	0.137	0.72 (0.40-1.1)	0.396
ACE n (%)	586 (40.5)	105 (40.1)	0.905	101 (42.8)	0.500	4 (15.4)	0.009
Aspirin n (%)	256 (17.7)	32 (12.2)	0.030	30 (12.7)	0.059	2 (7.7)	0.209
Smoker n (%)	195 (13.5)	34 (13.0)	0.830	30 (12.7)	0.752	4 (15.4)	0.764
Hypertensive n (%)	761 (52.6)	140 (53.4)	0.793	130 (55.1)	0.470	10 (38.5)	0.143

No DR – no diabetic retinopathy; Any DR – any diabetic retinopathy; BDR – background diabetic retinopathy; RDR – referable diabetic retinopathy; SD – standard deviation; IQ – Interquartile range; ACR – albumin: creatinine ratio; ACE – angiotensin converting enzyme inhibitors

Known duration of diabetes

Those who developed any DR and BDR were significantly younger at diagnosis of diabetes. However, whilst they had a longer known duration of diabetes those who developed RDR did not differ statistically from those who remained free of DR, may be due to the small numbers within this group (Table 6.4.3, page 231). There was a significant difference in the survival curves for the incidence of any DR and BDR in respects to the known duration of diabetes, subdivided as <5 years, 5-9 years and ≥ 10 years (Figure 6.4.3). Those with the longest known duration of diabetes i.e. >10 years, had the poorest prognosis with the survival curves for the incidence of any DR and BDR, with those with the shortest duration having the best prognosis.(Figure 6.4.3a,b). For the incidence of RDR those with a duration of diabetes of 5-9 years and ≥ 10 years had a similar prognosis, with those with a duration of diabetes <5 years having the best prognosis (Figure 6.4.3c). In the Cox regression analysis, after adjusting for age at diagnosis, gender, ethnicity, and baseline HbA_{1c} level, increased known duration of diabetes was significantly associated with the development of any DR, BDR and RDR (Table 6.4.4, page 234). Those persons with a known duration of diabetes of 5-9 years had a 2.9-fold increased risk of developing RDR when compared to those with a duration of diabetes of <5 years. This risk however decreased to 2.4-fold for the development of RDR in persons with a known duration of diabetes of ≥ 10 years compared to <5 years again this may be due to the small numbers within this group.

Figure 6.4.3: Kaplan-Meier survival curves for the development of a) any DR, b) BDR and c) RDR by known duration of diabetes in persons with T2DM



		Any DR							BDR							RDR						
		1	2	3	4	5	6	7	1	2	3	4	5	6	7	1	2	3	4	5	6	7
<5 years	Number at risk	843	614	419	278	171	82	20	839	612	418	297	171	82	20	851	633	442	303	192	97	26
	Number of cases	14	37	60	72	82	87	92	12	33	55	66	76	81	86	2	2	3	4	4	5	6
5-10 years	Number at risk	400	309	225	156	102	60	12	387	303	223	156	102	57	12	402	330	251	184	127	71	16
	Number of cases	8	35	56	65	69	74	77	8	28	45	52	56	61	64	0	3	7	7	9	12	12
>10 years	Number at risk	301	208	153	108	76	42	14	295	203	150	106	75	41	14	307	228	182	136	101	59	19
	Number of cases	8	39	62	72	78	87	90	7	37	58	67	72	81	83	0	2	3	4	4	6	7

6.4.4: Univariate and Multivariate Cox regression analysis for the incidence of any DR, BDR and RDR in persons with T2DM.

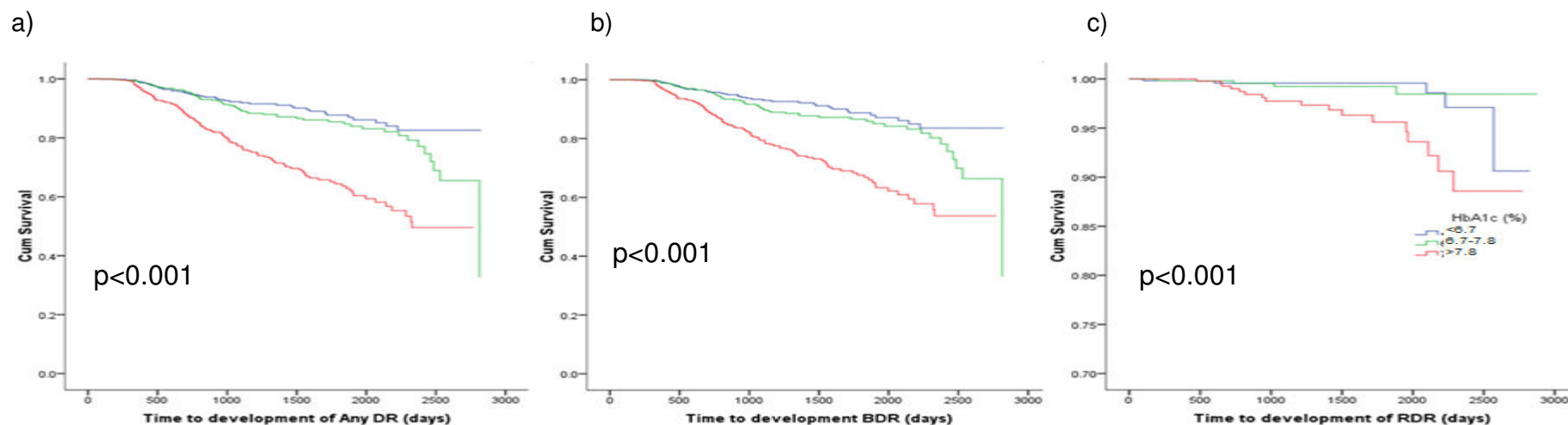
	<i>Any DR</i>		<i>BDR</i>		<i>RDR</i>	
	Crude HR (95% CI)	Adjusted HR (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)
Age at diagnosis of diabetes:						
<45 (459)	1.81 (1.25, 2.62)	0.79 (0.55, 1.13)	1.70 (1.16, 2.50)	0.77 (0.52, 1.13)	3.39 (0.75, 15.35)	0.82 (0.30, 2.25)
45-50 (337)	1.23 (0.81, 1.86)	0.82 (0.59, 1.15)	1.14 (0.74, 1.76)	0.82 (0.57, 1.16)	2.46 (0.49, 12.23)	0.84 (0.31, 2.24)
51-60 (520)	1.13 (0.77, 1.67)	0.93 (0.61, 1.41)	1.07 (0.72, 1.61)	0.98 (0.63, 1.52)	1.97 (0.41, 9.47)	0.56 (0.11, 2.72)
>60 (379)	1.00	1.00	1.00	1.00	1.00	1.00
Female	0.83 (0.64, 1.09)	0.79 (0.55, 1.13)	0.79 (0.58, 1.04)	0.72 (0.53, 0.97)	1.62 (0.74, 3.53)	1.30 (0.59, 2.89)
Non-Caucasians (433)	1.53 (1.17, 1.99)	1.26 (0.94, 1.69)	1.49 (1.13, 1.97)	1.23 (0.90, 1.69)	2.17 (0.98, 4.78)	1.51 (0.66, 3.49)
Known duration of diabetes						
<5 (953)	1.00	1.00	1.00	1.00	1.00	1.00
5-10 (531)	1.82 (1.37, 2.40)	1.60 (1.19, 2.15)	1.68 (1.25, 2.26)	1.49 (1.09, 2.03)	3.55 (1.38, 9.17)	2.94 (1.12, 7.70)
>10 (225)	2.63 (1.91, 3.63)	2.27 (1.60, 3.22)	2.63 (1.88, 3.68)	2.27 (1.58, 3.28)	2.63 (0.80, 8.66)	2.38 (0.70, 8.05)
HbA _{1c} (%)						
≤6.70 (550)	1.00	1.00	1.00	1.00	1.00	1.00
6.71-7.80 (530)	1.33 (0.91, 1.94)	1.24 (0.85, 1.82)	1.40 (0.94, 2.08)	1.32 (0.88, 1.97)	0.77 (0.21, 2.85)	0.65 (0.17, 2.45)
>7.80 (533)	3.31 (2.37, 4.64)	2.94 (2.08, 4.16)	3.32 (2.32, 4.75)	3.03 (2.10, 4.37)	3.79 (1.40, 10.28)	2.62 (0.93, 7.40)
Total Cholesterol (≥4.90) (454)	0.77 (0.54, 1.09)	N/A	0.77 (0.53, 1.11)	N/A	0.70 (0.24, 2.01)	N/A
ACE inhibitors (691)	1.02 (0.80, 1.31)		1.14 (0.88, 1.48)		0.28 (0.10, 0.80)	
ACR	1.02 (1.00, 1.04)		1.02 (1.00, 1.04)		0.92 (0.74, 1.14)	
Hypertension (901)	1.04 (0.81, 1.33)	N/A	1.11 (0.86, 1.44)	N/A	0.55 (0.25, 1.22)	N/A
Smoker (229)	0.98 (0.68, 1.41)	N/A	0.97 (0.66, 1.43)	N/A	1.18 (0.41, 3.41)	N/A
Aspirin (288)	1.20 (0.83, 1.75)		1.27 (0.86, 1.88)		1.07 (0.24, 4.74)	

N/A - variables were not included in the multivariate analysis

Glycaemic control

Those developing DR (any, BDR and RDR) had a significantly higher HbA_{1c} at the time of first screening than those who remained free of DR (Table 6.4.3, page 231). There was a significant difference in the survival curves for the incidence of any DR, BDR and RDR according to baseline HbA_{1c} level with those with an HbA_{1c} of >7.8% had much worse survival curves compared to those with an HbA_{1c} of 6.7-7.8 and ≤6.7% (Figure 6.4.4). Increased HbA_{1c} levels were also significantly associated with the incidence of any DR, BDR and RDR in the Cox regression analysis after adjusting for age at diagnosis, gender, ethnicity and known duration of diabetes (Table 6.4.4, page 234). Those persons with a baseline HbA_{1c} of 6.7-7.8% did not have a significantly increased risk of developing any DR, BDR or RDR compared to those with an HbA_{1c} of <6.7%. In comparison, those persons with an HbA_{1c} of >7.8% had a 2.9-, 3.0- and 2.6-fold increased risk of developing any DR, BDR and RDR respectively compared to those with a HbA_{1c} level of <6.7%.

Figure 6.4.4: Kaplan-Meier survival curves for the development of a) any DR, b) BDR and c) RDR by HbA_{1c} level at first screening in persons with T2DM

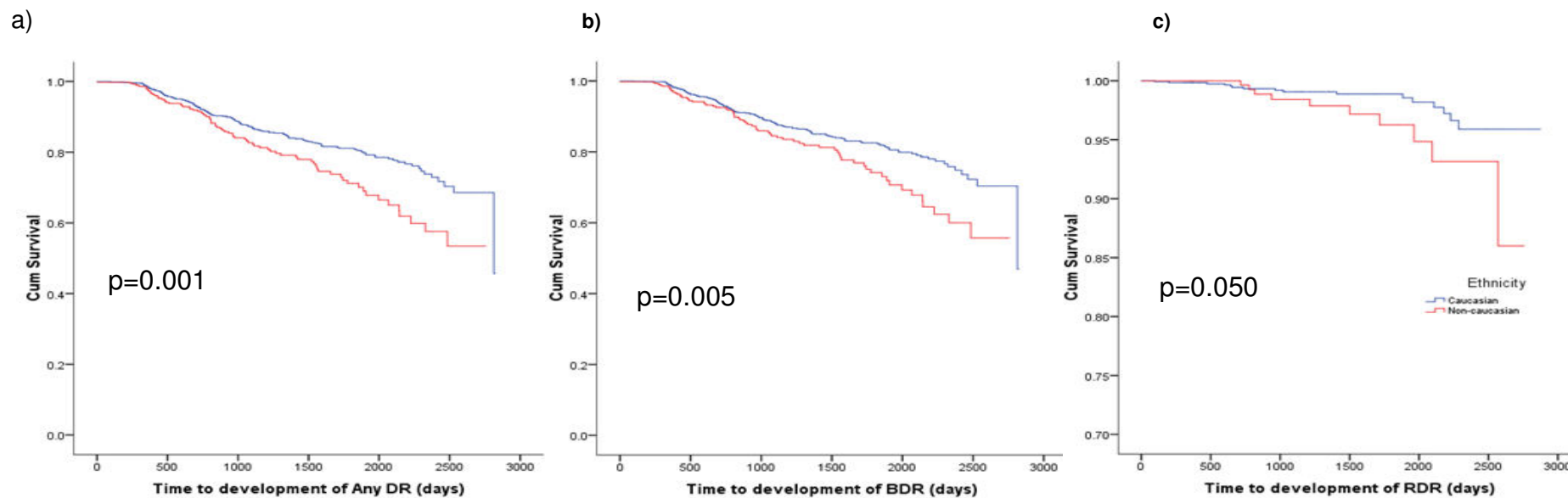


		Any DR							BDR							RDR						
		1	2	3	4	5	6	7	1	2	3	4	5	6	7	1	2	3	4	5	6	7
≤6.7%	Number at risk	499	360	262	185	121	66	15	495	359	262	185	121	66	15	502	368	275	198	136	78	18
	Number of cases	5	23	32	35	41	45	46	4	19	27	30	36	40	41	1	2	2	2	2	3	4
6.71-7.80%	Number at risk	486	380	273	185	122	71	17	483	377	272	184	122	71	17	488	394	293	205	139	82	21
	Number of cases	5	20	41	48	51	55	62	4	19	38	45	47	51	58	1	1	3	3	3	4	4
>7.81%	Number at risk	483	336	222	142	87	36	10	467	327	217	141	102	35	10	493	369	260	186	122	55	17
	Number of cases	13	57	90	109	118	127	130	12	49	78	93	86	111	113	0	4	8	10	12	16	17

Ethnicity

There were significantly more non-Caucasians who developed any DR compared to those who remained free of DR. However, there was no significant difference between those who remained free of DR and those who developed BDR or RDR (Table 6.4.3, page 231). Over the duration of the study, there was a significant difference between the survival curves of Caucasians and non-Caucasians for the incidence of any DR and BDR with non-Caucasians having a worse prognosis (Figure 6.4.5). For the incidence of RDR, non-Caucasians again appeared to have the worst prognosis but the difference just failed to reach significance. In the Cox regression analysis, after adjusting for age at diagnosis, gender, known duration of diabetes and baseline HbA_{1c} level, there was a trend for non-Caucasians to be at an increased risk of developing any DR, BDR and RDR however this did not reach significance (Table 6.4.5, 234).

Figure 6.4.5: Kaplan-Meier survival curves for the development of a) any DR, b) BDR and c) RDR by ethnicity in persons with T2DM



		Any DR							BDR							RDR						
		1	2	3	4	5	6	7	1	2	3	4	5	6	7	1	2	3	4	5	6	7
Caucasian	Number at risk	1160	875	621	419	278	148	36	1147	868	618	417	277	147	36	1172	920	678	477	330	185	44
	Number of cases	19	80	125	147	158	170	178	16	71	112	133	143	155	162	2	6	9	10	10	14	16
Non-Caucasian	Number at risk	385	257	177	124	752	34	10	375	251	174	124	72	34	10	389	272	199	147	91	43	17
	Number of cases	11	31	53	62	71	78	81	11	27	46	52	61	68	71	0	1	4	5	7	9	9

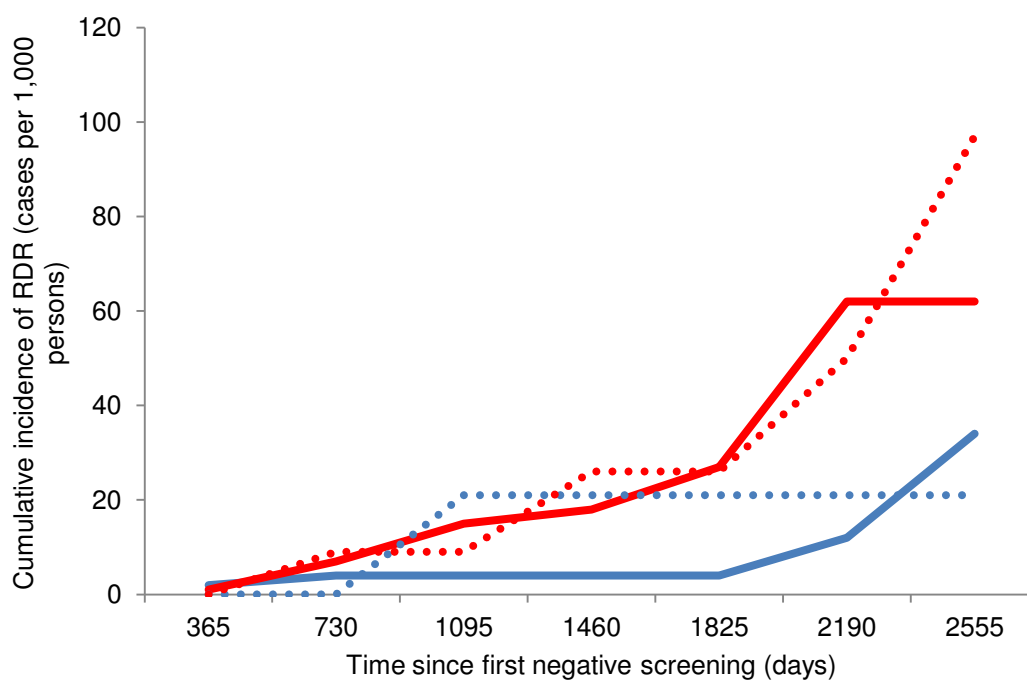
6.4.1.3 Screening intervals for persons with T2DM

In view of the findings above, which indicate that an increasing known duration of diabetes and a higher HbA_{1c} at first screening appears to be the most important explanatory variables for predicting the development of DR. These factors were then used to assess the cumulative incidence of RDR over the study. Known duration of diabetes was stratified into the following subgroups ≤ 10 years (short duration) and >10 years (long duration). HbA_{1c} was stratified into $\leq 7.0\%$ (low HbA_{1c}) and $>7.0\%$ (high HbA_{1c}) (Figure 6.4.6).

Known duration of diabetes and glycaemic control

Those persons with a high HbA_{1c} level and long known duration of diabetes at baseline had the highest seven year cumulative incidence of RDR (cases per 1,000 persons) at 97 cases (95% CI 79.8, 114.2) compared to 34 cases (95% CI 31.6, 36.4) with a low HbA_{1c} and short duration of diabetes and 21 cases (95% CI 16.0, 26.0) with a low HbA_{1c} and a long duration and 62 cases with a high HbA_{1c} and a short duration of diabetes (Figure 6.4.6) The one and two year cumulative incidence of RDR in those with a low HbA_{1c} level was 2 (95% CI 1.99, 2.01) and 4 cases (95% CI 3.98, 4.01) respectively with a short duration. There was no new cases of RDR in those with a low HbA_{1c} level and a long duration before 3 years. In those with a high HbA_{1c}, the one and two year cumulative incidence of RDR was 1 (95% CI 0.99, 1.00) and 7 cases (95% CI 6.97, 7.02) respectively with a short duration and 0 and 9 cases (95% CI 8.8, 9.2) respectively in those with a long duration. Therefore, it may be safe to screen persons with a low baseline HbA_{1c} level and a short known duration of diabetes once every 5 years, those with a low HbA_{1c} and a long known duration of diabetes once every three years, and those with a high HbA_{1c} level irrespective of duration of diabetes once every 2 years.

Figure 6.4.6: Cumulative incidence of RDR sub-grouped by HbA_{1c} level at first screening and known duration of diabetes in persons with T2DM



	Category	Total n	cases n	*1 year	*2 year	*3 year	*4 year	*5 year	*6 year	*7 year
—	≤7.0% ≤10 years	644	5	2	4	4	4	4	12	34
—	>7.0% ≤10 years	71	1	1	7	15	18	27	62	62
.....	≤7.0% >10 years	745	15	0	0	21	21	21	21	21
.....	>7.0% >10 yea	140	4	0	9	9	26	26	50	97

*Incidence is cases per 1,000 persons

6.4.1.4 Summary of Main Findings for persons with T2DM

- Only one person with T2DM without DR at first screening developed PDR during the course of the seven year study period.
- The seven year cumulative incidence of any DR, BDR and RDR was 351, 331 and 47 cases.
- After adjusting for age at diagnosis of diabetes, gender and ethnicity, increased duration (known) of diabetes and deteriorating glycaemic control (HbA_{1c}) were both associated with increasing incidence of any DR, BDR and RDR.
- Ethnicity was not independently associated with the incidence of RDR when adjusted for HbA_{1c} and known duration of diabetes. However, the numbers of non-Caucasians within this group were very small.
- The screening interval in persons with T2DM was stratified based on known duration of diabetes and glycaemic control.
- Those with a $HbA_{1c} \leq 7.0\%$ and a duration of diabetes of ≤ 10 years could have a screening interval of once every two or three years with 2 or 4 cases per 1,000 persons respectively at risk of a delayed diagnosis of RDR.
- Those with a $HbA_{1c} \leq 7\%$ and a duration of diabetes >10 years could have a screening interval of once every three years as there were no cases of RDR until 3 years after a negative screening.
- Those with a $HbA_{1c} > 7\%$ irrespective of duration of diabetes could have a screening interval of once every two years with only 1 case per 1,000 persons at risk of a delayed diagnosis of RDR.

6.4.2 T1DM

6.4.2.1 Incident DR in persons with T1DM

927 (39.1%) persons with T1DM did not have DR at first screening. Of these 31.3% (290) did not undergo a repeat screening within the seven year study period. 14.1% (41) were not eligible for a repeat screening, as this would have been within 12 months of the first event, and for an additional 2 persons the date of first screening was unavailable. The remainder 85.9% (247) although eligible for repeat screening and were within the defined time frame screening, unfortunately did not occur for unknown reasons. Those who did not undergo a second screening event had a significantly shorter duration of diabetes and a higher HbA_{1c} level compared to those who did have a second screening event. No other significant differences were seen as outlined in Table 6.4.5. Of those included in the analysis (637) the majority were male (54%), Caucasian (81.8%), with a mean age at diagnosis of 23.5 years, median duration of diabetes of 7 years and a median HbA_{1c} of 8.1% at entry into the study (Table 6.4.5).

Table 6.4.5: Baseline characteristics between persons with T1DM who did undergo a repeat screening event and those who were otherwise eligible but did not.

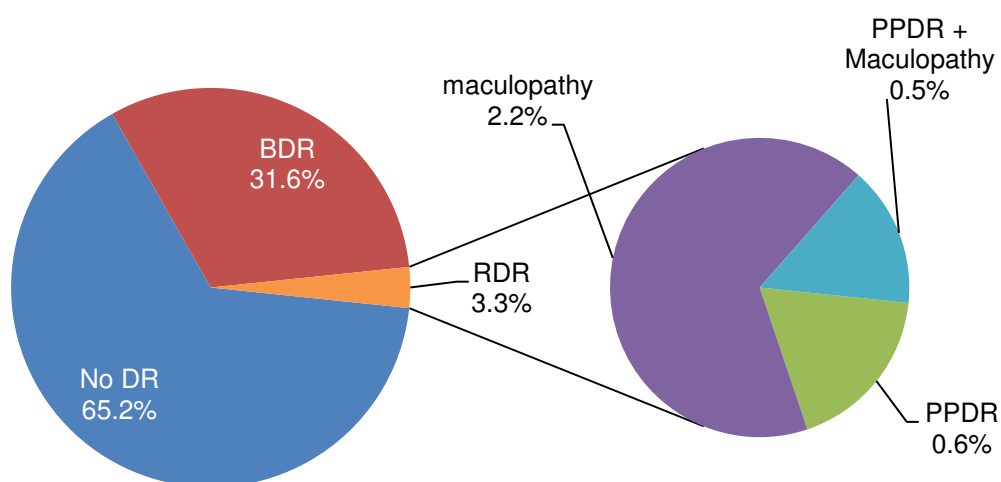
	<i>No Second screening (247)</i>	<i>Included (637)</i>	<i>p value</i>
Age years mean (SD)	31.9 (16.9)	33.5 (15.3)	0.261
Gender: n (%)			0.526
Male	127 (51.4)	344 (54.0)	
Female	119 (48.2)	293 (46.0)	
Ethnicity: n (%)			0.198
Caucasian	192 (77.7)	521 (81.8)	
Indigenous African	22 (8.9)	51 (8.0)	
Asian	19 (7.7)	47 (7.4)	
Mixed Race	13 (5.3)	16 (2.5)	
Duration yrs median (IQR)	5.0 (2.0-9.0)	7.0 (4.0-13.0)	<0.001
Age at diagnosis yrs mean (SD)	24.0 (15.7)	23.5 (14.0)	0.624
HbA _{1c} % median (IQR)	8.7 (7.5-10.6)	8.1 (7.0-9.5)	<0.001
Total Cholesterol mmol/L mean (SD)	5.2 (1.4)	5.0 (1.0)	0.166
ACR median (IQR)	0.91 (0.42-1.58)	0.68 (0.37-1.4)	0.088
Other therapies: n (%)			
Aspirin	5 (2.0)	10 (1.6)	0.639
ACE	20 (8.1)	73 (11.5)	0.144
Hypertension n (%)	24 (9.7)	84 (13.2)	0.157
Current Smokers n (%)	47 (19.0)	107 (16.8)	0.433

SD – Standard Deviation; n – total number; IQR – Interquartile range; ACR – albumin:creatinine ratio; ACE – angiotension converting enzymes; yrs - years

During the seven year study period a total of 454 (71.3%) persons had three screening events, 323 (50.9%) had four, 228 (36.0%) had five, 159 (25.1%) had six, 82 (12.9%) had seven, 23 (3.6%) had eight, 4 (0.7%) had nine and only 1 (0.2%) had ten screening events. The mean (SD) screening interval during the study period ranged from 1.2 (1.2) years between the first and second screening event to 0.6 (0.5) years between the seventh and eighth. During the study period, 34.8% (224) developed any DR, 31.6% (203) BDR and 3.3% (21) RDR (Figure 6.4.7). The

categories of RDR consisted of 0.6% (4) PPDR, 2.2% (14) maculopathy and 0.5% (3) PPDR with maculopathy. Noone developed PDR. Therefore, 65.2% (419) remained free of DR at their final screening event.

Figure 6.4.7: Incident DR during the seven year study period in persons with T1DM



No DR - No diabetic retinopathy; BDR - Background diabetic retinopathy, RDR - Referable diabetic retinopathy; PPDR - Pre-proliferative diabetic retinopathy;

The annual and cumulative incidence of any DR, BDR and RDR over the seven year study period is represented in Table 6.4.6. The annual incidence (cases per 1,000 persons) of any DR increased from 29 cases in the first year to 63 cases in the seventh year. The annual incidence of RDR increased from 2 cases in the first year to 5 cases in the seventh year. The seven year cumulative incidence of any DR was 536 cases, BDR 511 cases and RDR 50 cases.

Table 6.4.6: Incidence of any DR, BDR and RDR over the seven year study period in persons with T1DM

Any DR			
Time (yrs)	Number	Annual Incidence	Cum. Incidence (95% CI)
1	589	29.0	29.0 (28.9, 29.1)
2	427	134.0	163.0 (162.4, 163.6)
3	350	91.0	254.0 (252.9, 255.1)
4	257	65.0	319.0 (317.3, 320.7)
5	178	77.0	396.0 (393.4, 398.6)
6	113	77.0	473.0 (468.7, 477.3)
7	29	63.0	536.0 (518.6, 553.4)
BDR			
Time (yrs)	Number	Annual Incidence	Cum. Incidence (95% CI)
1	570	28.0	28.0 (27.9, 28.1)
2	416	124.0	152.0 (151.4, 152.6)
3	322	88.0	240.0 (238.9, 241.1)
4	253	66.0	299.0 (269.4, 300.6)
5	176	73.0	372.0 (369.4, 374.6)
6	113	73.0	445.0 (440.7, 449.3)
7	29	66.0	511.0 (493.5, 528.5)
RDR			
Time (yrs)	Number	Annual Incidence	Cum. Incidence (95% CI)
1	602	2.0	2.0 (1.99, 2.01*)
2	497	7.0	9.0 (8.96, 9.03*)
3	422	9.0	18.0 (17.9, 18.1)
4	357	7.0	25.0 (24.9, 25.1)
5	275	6.0	31.0 (30.8, 31.2)
6	186	14.0	45.0 (44.6, 45.5)
7	60	5.0	50.0 (48.8, 51.2)

Number - Number of persons at risk; Number of cases per 1,000 persons; Any DR – any diabetic retinopathy ; BDR – background diabetic retinopathy ; RDR – referable diabetic retinopathy ; cum incidence – cumulative incidence; Time - time since first negative screening event; Number - Number of cases remaining at risk; 95% CI – 95% confidence interval; yrs - years;* two decimal places provided due to the small difference in value

6.4.2.2 Risk factors for incident DR

The characteristics of those who developed any DR, BDR and RDR compared to those who remained free of DR are shown in Table 6.4.7. There were no significant differences between those without DR and those who developed any DR, BDR or RDR for age, gender, ACR, smoking status, hypertension, and ACE inhibitors or aspirin use. These were also not significant in Kaplan Meier and Cox regression analysis (Table 6.4.8, page 246). There were also no significant differences or associations between those without DR and those who developed BDR and RDR for total cholesterol.

Table 6.4.7: Baseline Characteristics of persons with T1DM who developed DR and those who remained free of DR

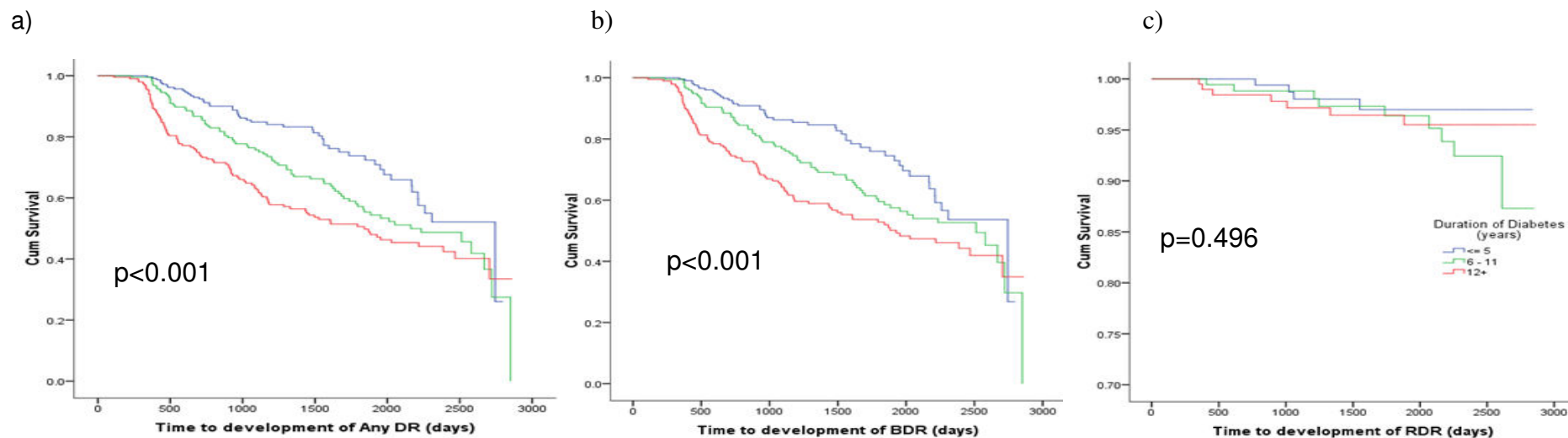
	<i>No DR (419)</i>	<i>Any DR (224)</i>	<i>p value No DR vs. Any DR</i>	<i>BDR (203)</i>	<i>p value No DR vs. BDR</i>	<i>RDR (21)</i>	<i>p value No DR vs. RDR</i>
Age years mean (SD)	33.9 (15.8)	32.9 (14.3)	0.475	32.4 (14.0)	0.275	38.2 (16.1)	0.164
Gender: n (%)			0.130		0.109		0.882
Male	217 (51.8)	130 (58.0)		119 (58.6)		11 (52.4)	
Female	202 (48.2)	94 (42.0)		84 (41.4)		10 (47.6)	
Ethnicity: n (%)			0.730		0.995		0.003
Caucasian	347 (82.8)	177 (79.7)		165 (82.1)		12 (57.1)	
Indigenous African	33 (7.9)	19 (8.6)		16 (8.0)		3 (14.3)	
Asian Indian	29 (6.9)	18 (8.1)		15 (7.5)		3 (14.3)	
Mixed Race	10 (2.4)	8 (3.6)		5 (2.5)		3 (14.3)	
Duration years median (IQ)	6.0 (3.0-12.0)	10.0 (6.0-17.0)	<0.001	10.0 (6.0-17.0)	<0.001	8.0 (5.5-15.5)	0.758
Age at diagnosis years mean (SD)	25.0 (14.5)	20.5 (12.4)	<0.001	19.8 (12.2)	<0.001	27.0 (13.2)	0.250
HbA _{1c} % median (IQ)	7.9 (6.9-9.4)	8.4 (7.4-9.9)	0.032	8.3 (7.3-9.6)	0.190	10.1 (7.9-11.6)	<0.001
Total Cholesterol mmol/l mean (SD)	4.9 (1.0)	5.2 (1.1)	0.030	5.1 (0.9)	0.096	5.9 (1.9)	0.200
ACR median (IQ)	0.71 (0.37-1.4)	0.63 (0.34-1.3)	0.830	0.62 (0.37-1.3)	0.820	1.2 (0.27-2.6)	0.956
ACE n (%)	42 (10.0)	33 (14.7)	0.076	29 (14.3)	0.117	4 (19.0)	0.284
Aspirin n (%)	7 (1.7)	3 (1.3)	0.746	3 (1.5)	0.858	0	0.558
Hypertensive n (%)	49 (11.7)	37 (16.5)	0.087	30 (14.8)	0.279	7 (33.3)	0.006
Smoker n (%)	69 (16.5)	38 (17.0)	0.872	34 (16.7)	0.930	4 (19.0)	0.763

No DR - no diabetic retinopathy; any DR - any diabetic retinopathy; BDR – background diabetic retinopathy; RDR – referable diabetic retinopathy; SD – standard deviation; IQ Interquartile range; ACR – albumin:creatinine ratio; ACE – angiotensin converting enzyme inhibitor

Duration of diabetes

Those who developed any DR and BDR compared to those without DR had a significantly longer duration of diabetes (Table 6.4.7, page 243). Although those with RDR had a longer duration of diabetes compared to those without DR, this did not reach significance. There were significant differences in the survival curves for the incidence of any DR, and BDR according to the duration of diabetes, but not RDR (Figure 6.4.8). Those with a duration of diabetes of ≥ 12 years had the poorest prognosis compared to those with a duration of diabetes of ≤ 5 years in respect to the development of any DR or BDR. There was no significant differences in the survival curves for duration of diabetes and the time until RDR developed, however, the numbers in this group were limited. Increased duration of diabetes had the strongest association with the incidence of any DR, BDR and RDR in Cox regression analysis after adjusting for age at diagnosis of diabetes, gender, ethnicity, HbA_{1c} and hypertension (Table 6.4.8, page 246). Those persons with a duration of diabetes of 6-11 years had a 1.5 fold increased risk of developing any DR and BDR and a 3.6 fold increased risk of developing RDR compared to those with a duration of diabetes of ≤ 5 years. Those persons with a duration of diabetes of ≥ 12 years had a 2.3, 2.2 and 4.9 fold increased risk of developing any DR, BDR and RDR respectively compared to those with a duration of diabetes of ≤ 5 years.

Figure 6.4.8: : Kaplan-Meier survival curves for the development of a) any DR, b) BDR and c) RDR by duration of diabetes in persons with T1DM



		Any DR							BDR							RDR						
		1	2	3	4	5	6	7	1	2	3	4	5	6	7	1	2	3	4	5	6	7
≤ 5 years	Number at risk	221	158	121	91	54	31	5	217	155	109	90	54	31	4	221	171	136	105	70	42	11
	Number of cases	1	16	27	29	38	45	49	1	15	25	26	34	41	45	0	0	3	3	4	4	4
6-11 year	Number at risk	187	137	110	88	64	41	13	178	132	105	85	62	41	13	188	157	140	120	98	70	27
	Number of cases	1	25	40	52	64	71	73	1	21	36	46	57	62	64	0	2	2	4	5	7	8
≥ 12 year	Number at risk	181	132	99	81	60	41	12	175	129	97	78	60	41	12	194	169	146	132	107	74	22
	Number of cases	16	51	68	78	86	92	95	15	47	63	74	79	85	88	1	3	5	6	6	7	7

Table 6.4.8: Multivariate Cox regression for the development of any DR, BDR and RDR in persons with T1DM

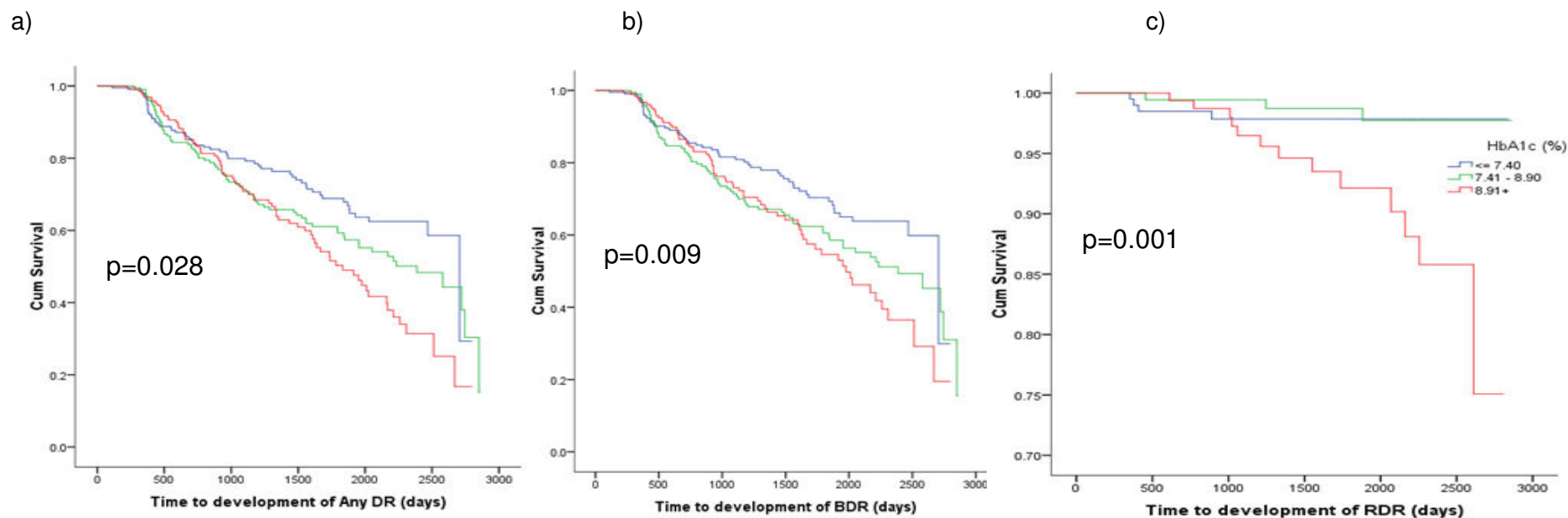
	<i>Any DR (224)</i>		<i>BDR (213)</i>		<i>RDR (21)</i>	
	Crude	Adjusted	Crude	Adjusted	Crude	Adjusted
Female (296)	0.89 (0.68, 1.16)	0.87 (0.66, 1.15)	0.87 (0.66, 1.15)	0.84 (0.63, 1.12)	1.23 (0.51, 2.96)	1.71 (0.68, 4.29)
Non-Caucasians (117)	1.44 (1.04, 2.00)	1.68 (1.20, 2.35)	1.31 (0.92, 1.86)	1.59 (1.10, 2.30)	4.47 (1.85, 10.80)	4.67 (1.73, 12.60)
Age at diagnosis:						
≤12 (179)	2.37 (1.59, 3.53)	2.40 (1.55, 3.71)	2.80 (1.81, 4.34)	2.73 (1.70, 4.37)	0.46 (0.14, 1.59)	0.46 (0.11, 1.84)
13-22 (144)	1.68 (1.09, 2.58)	1.73 (1.10, 2.73)	1.93 (1.21, 3.09)	1.91 (1.17, 3.12)	0.42 (0.11, 1.63)	0.57 (1.34, 2.40)
23-33 (164)	1.72 (1.13, 2.62)	1.93 (1.25, 2.98)	1.93 (1.22, 3.05)	2.05 (1.28, 3.30)	0.75 (0.25, 2.24)	0.95 (0.31, 2.93)
≥34 (153)	1.00	1.00	1.00	1.00	1.00	1.00
Duration of diabetes						
≤5 (242)	1.00	1.00	1.00	1.00	1.00	1.00
6-11 (199)	1.62 (1.13, 2.31)	1.53 (1.05, 2.23)	1.59 (1.09, 2.32)	1.49 (1.01, 2.21)	2.01 (0.61, 6.55)	3.62 (1.02, 12.82)
≥12 (202)	2.11 (1.50, 2.98)	2.28 (2.56, 3.33)	2.14 (1.49, 3.05)	2.24 (1.51, 3.32)	1.48 (0.43, 5.08)	4.88 (1.09, 21.75)
HbA _{1c}						
≤7.40 (208)	1.00	1.00	1.00	1.00	1.00	1.00
7.41-8.90 (207)	1.35 (0.96, 1.90)	1.18 (0.84, 1.68)	1.40 (0.98, 1.98)	1.22 (0.85, 1.75)	0.75 (0.17, 3.34)	0.55 (0.12, 2.58)
>8.90 (201)	1.69 (1.21, 2.37)	1.75 (1.22, 2.50)	1.61 (1.13, 2.31)	1.67 (1.14, 2.43)	4.17 (1.36, 12.84)	5.02 (1.48, 16.98)
Total Cholesterol						
≤4.43 (83)	1.00	n/a	1.00	n/a	1.00	n/a
4.44-5.38 (83)	1.80 (1.02, 3.17)		1.96 (1.09, 3.53)		0.47 (0.04, 5.20)	
≥5.39 (82)	1.61 (0.92, 2.83)		1.56 (0.85, 2.84)		2.25 (0.44, 11.60)	
ACR ratio	1.03 (0.99, 1.08)		1.04 (0.99, 1.08)		1.02 (0.83, 1.24)	
ACE inhibitors (75)	1.48 (1.02, 2.15)	n/a	1.43 (0.96, 2.12)	n/a	2.00 (0.67, 6.00)	n/a
Hypertensive (86)	1.42 (1.00, 2.02)	1.56 (1.06, 2.30)	1.26 (0.86, 1.86)	1.41 (0.93, 2.15)	3.81 (1.52, 9.55)	3.30 (1.17, 9.31)
Smoking status (107)	1.06 (0.75, 1.51)	n/a	1.04 (0.72, 1.51)	n/a	1.31 (0.44, 3.92)	n/a

n/a - variables were excluded from the multivariate analysis

Glycaemic control

Those who developed any DR and RDR had a significantly higher HbA_{1c} at first screening (8.4% and 10.1% respectively) than those who remained free of DR (7.8%) (Table 6.4.7, page 243). There was also a significant difference in the survival curves for any DR, BDR and RDR according to baseline HbA_{1c} (Figure 6.4.9). Those with an HbA_{1c} of >8.9% had the worst 'survival' curves for the incidence of any DR, BDR and RDR compared to those with an HbA_{1c} of 7.41-8.9% or ≤7.4. However, the survival rates for those with an HbA_{1c} of 7.41-8.9% and >8.9 were similar until approximately 4 years for any DR, and 4.8 years for BDR. This separation in survival curves appeared earlier after approximately 2.8 years for the incidence of RDR. Increasing HbA_{1c} levels at first screening were associated with an increased risk of developing any DR, BDR and RDR in the Cox regression analysis after adjusting for age at diagnosis of diabetes, gender, ethnicity, duration of diabetes and hypertension (Table 6.4.8, page 246). Those persons with a baseline HbA_{1c} level of 7.4-8.9% did not differ significantly in their risk of developing any DR, BDR or RDR compared to those with a HbA_{1c} ≤7.4%. However, those with an initial HbA_{1c} >8.9% had a 1.8-fold increased risk of developing any DR, a 1.7-fold increased risk of developing BDR and a 5-fold increased risk of developing RDR compared to those with a baseline HbA_{1c} level of ≤7.4%.

Figure 6.4.9: Kaplan-Meier survival curves for the development of a) any DR, b) BDR and c) RDR by HbA_{1c} level at first screening in persons with T1DM

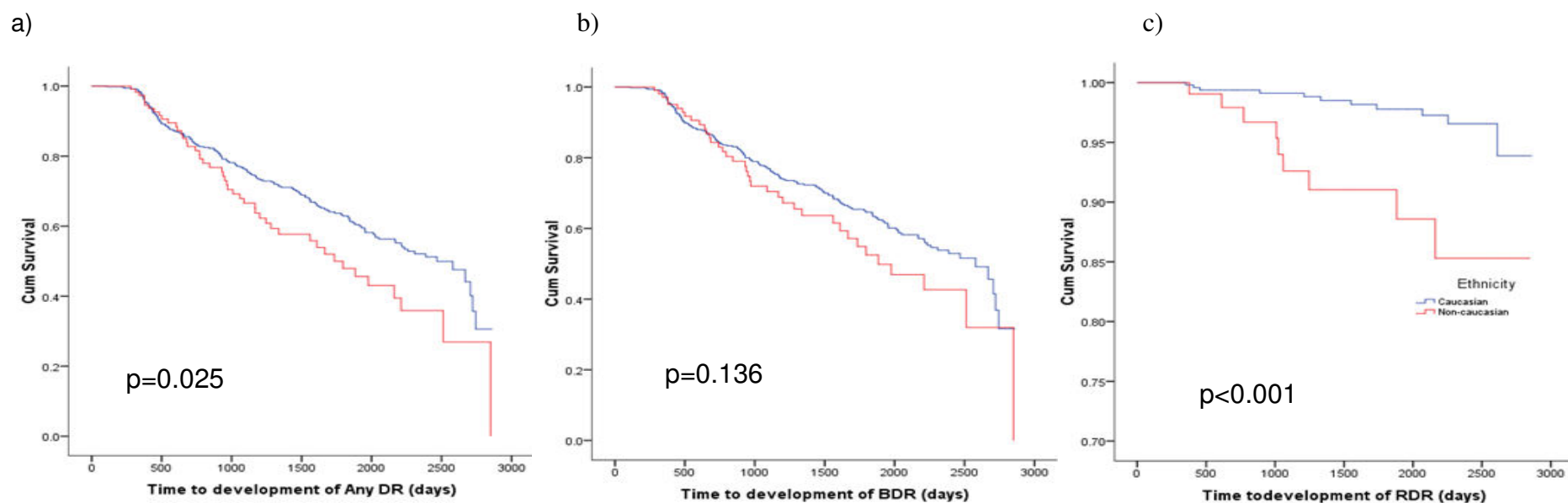


		Any DR							BDR							RDR						
		1	2	3	4	5	6	7	1	2	3	4	5	6	7	1	2	3	4	5	6	7
≤7.4 %	Number at risk	193	144	117	95	69	47	7	190	144	117	95	69	47	7	199	166	142	123	99	74	20
	Number of cases	7	30	37	44	51	57	58	6	26	33	40	47	53	54	1	3	4	4	4	4	4
7.41-8.9%	Number at risk	192	132	103	87	64	41	14	189	130	101	87	64	41	14	196	159	143	131	105	64	23
	Number of cases	5	33	49	57	65	71	74	5	32	48	54	62	68	71	0	1	1	2	2	3	3
>8.9 %	Number at risk	183	135	96	66	37	20	4	170	126	90	60	36	20	4	187	155	123	92	63	42	13
	Number of cases	6	28	47	56	67	75	79	6	24	40	48	56	62	66	0	1	5	7	9	11	12

Ethnicity

Significantly more non-Caucasians developed RDR than any other ethnic group (Table 6.4.7, page 243). There was a significant difference between the survival curves for ethnicity and the incidence of any DR and RDR, but not for the incidence of BDR (Figure 6.4.10). Non-Caucasians had the worst prognosis for the incidence of any DR, BDR and RDR. Non-Caucasians were at 1.7-, 1.6- and 4.7-fold increased risk of developing any DR, BDR and RDR respectively compared to Caucasians based on the Cox regression analysis after adjusting for age at diagnosis of diabetes, gender, duration of diabetes, HbA_{1c} and hypertension (Table 6.4.8, page 246).

Figure 6.4.10: Kaplan-Meier survival curves for the development of a) any DR, b) BDR and c) RDR by Ethnicity in persons with T1DM



		Any DR							BDR							RDR						
		1	2	3	4	5	6	7	1	2	3	4	5	6	7	1	2	3	4	5	6	7
Caucasian	Number at risk	483	356	280	224	156	102	26	473	351	275	221	155	102	26	496	415	357	307	237	161	53
	Number of cases	15	75	105	126	147	164	171	14	69	99	118	137	153	160	1	3	4	6	8	9	10
Non-Caucasian	Number at risk	106	71	50	33	22	11	3	97	65	47	32	21	11	3	107	82	65	50	38	25	7
	Number of cases	3	17	30	36	41	44	46	3	14	24	28	33	35	37	0	2	6	7	7	9	9

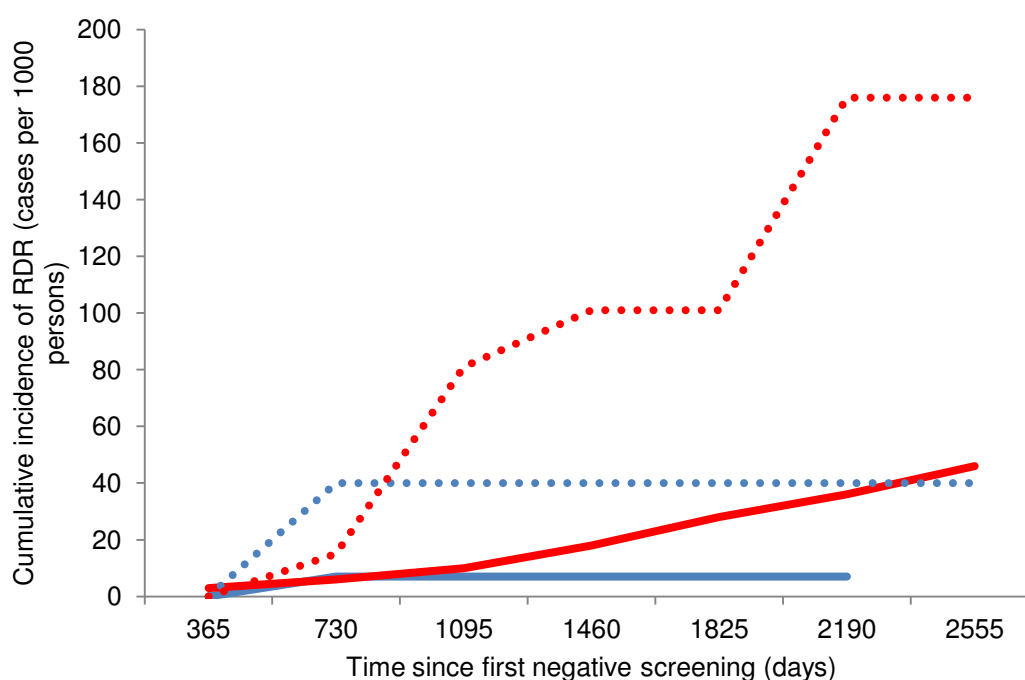
6.4.2.3 Screening intervals for persons with T1DM

As the risk factors duration of diabetes, HbA_{1c} and ethnicity were the most important explanatory variables for predicting the development of DR these were then used to assess the cumulative incidence of RDR. Caucasians and non-Caucasians were stratified into low HbA_{1c} ($\leq 7.0\%$) and high HbA_{1c} ($> 7.0\%$) groups at first screening (Figure 6.4.11), and also according to the duration of diabetes i.e. short (≤ 10 years) and long (> 10 years) duration of diabetes (Figure 6.4.12). Low and high HbA_{1c} level were further stratified according to short and long duration of diabetes i.e. 10 years and below and over 10 years respectively (Figure 6.4.13).

Ethnicity and glycaemic control

The seven year cumulative incidence of RDR (cases per 1,000 persons) in those with a high HbA_{1c} was 176 cases (95% CI 128.6, 223.4) in non-Caucasian persons compared to a much lower incidence in Caucasians at 46 cases (95% CI 43.5, 48.5) (Figure 6.4.11). The one and two year cumulative incidence in those persons with a low HbA_{1c} was 0 and 7 cases (95% CI 6.9, 7.1) respectively for Caucasians and was 0 and 40 cases (95% CI 35.3, 44.7) in non-Caucasians respectively. In those with a high HbA_{1c} the one and two year incidence of RDR was 3 (95% CI 2.98, 3.02) and 6 cases (95% CI 5.95, 6.04) respectively in Caucasians and surprisingly 0 and 15 cases (95% CI 14.6, 15.4) in non-Caucasians respectively. The lower incidence of RDR in non-Caucasians with a high HbA_{1c} may be due to the small number of persons who developed RDR as well as the small numbers of non-Caucasians. Therefore, both Caucasians and non-Caucasians could undergo screening once every two years with minimal risk of 3 cases per 1,000 persons, irrespective of glycaemic control.

Figure 6.4.11: Cumulative incidence of RDR for low and high HbA_{1c} levels and ethnicity in persons with T1DM



	Category	Total n	RDR cases n	*1 year	*2 years	*3 years	*4 years	*5 years	*6 years	*7 years
—	C ≤7.0%	132	1	0	7	7	7	7	7	7
—	C >7.0%	366	10	3	6	10	18	28	36	46
.....	NC ≤7.0%	24	1	0	40	40	40	40	40	40
.....	NC >7.0%	85	7	0	15	81	101	101	176	176

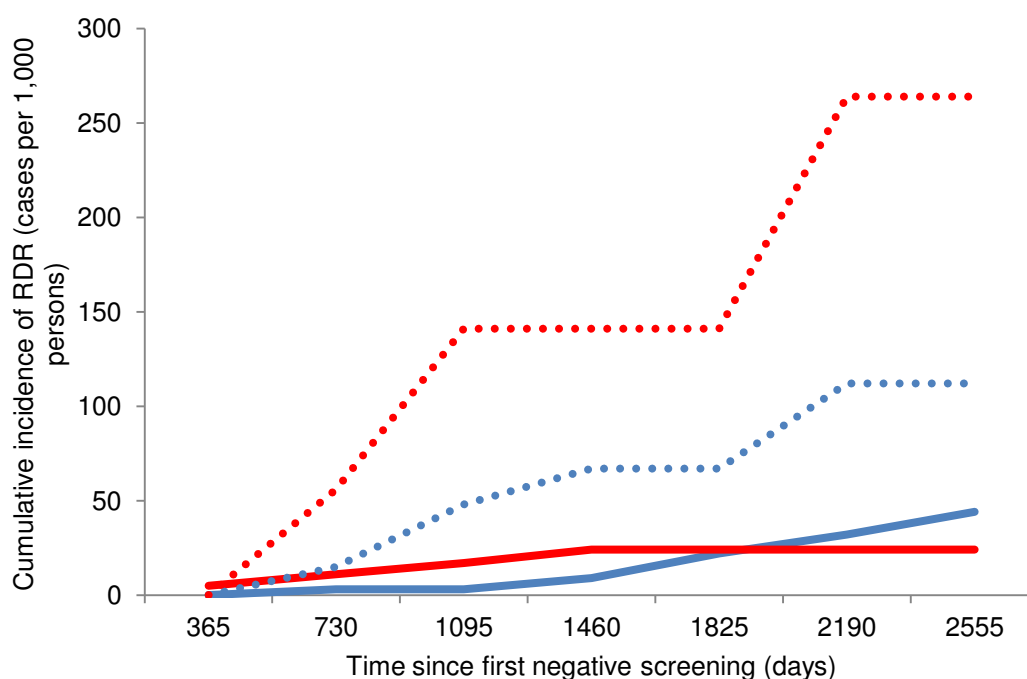
Key: C - Caucasian; NC - Non-Caucasian; *incidence if cases per 1,000 persons

Ethnicity and duration of diabetes

The seven year cumulative incidence of RDR in those with a long duration of diabetes was lower in Caucasians at 24 (95% CI 22.5, 25.5) compared to non-Caucasians at 264 (95%CI 137.1, 390.9) (Figure 6.4.12). The one and two year cumulative incidence of RDR in those with a short duration of diabetes was 0 and 3 cases (95% CI 2.98, 3.02) in Caucasians and 0 and 15 cases (95% CI 14.6, 15.4) in non-Caucasian. In those with a long duration of diabetes the one and two year incidence of RDR was 5 (95% CI 4.95, 5.05) and 11 cases (95% CI 10.9, 11.1) in Caucasians and 0 and 56 cases (95% CI 48.0, 64.0) in non-Caucasian. Therefore, Caucasians with a long duration of diabetes, and non-Caucasians irrespective of

duration of diabetes, could be screened once every two years with only 5 cases at risk of a delayed diagnosis of RDR. Caucasians with a short duration of diabetes could be screened once every three years with 3 cases at an risk of a delayed diagnosis of RDR.

Figure 6.4.12: Cumulative incidence of RDR by duration of diabetes and ethnicity in persons with T1DM



	Category	Total n	RDR cases n	*1 year	*2 years	*3 years	*4 years	*5 years	*6 years	*7 years
—	C ≤10 years	327	7	0	3	3	9	22	32	44
—	C >10 years	191	4	5	11	17	24	24	24	24
.....	NC ≤10 years	93	5	0	15	48	67	67	112	112
.....	NC >10 years	21	3	0	56	141	141	141	264	264

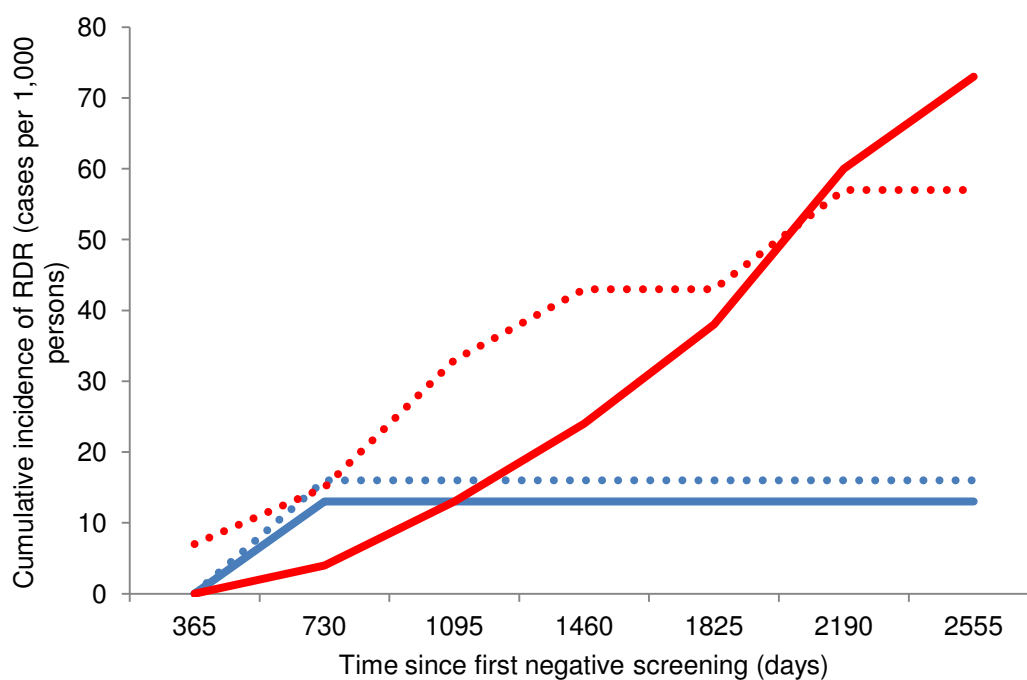
Key: C - Caucasian; NC - Non-Caucasian; *Incidence of DR is cases per 1,000 persons

Duration of diabetes and glycaemic control

If duration of diabetes and baseline HbA_{1c} were combined then those with a long duration of diabetes and high HbA_{1c} level had the highest incidence of RDR initially with a 1 year incidence of RDR at 7 cases per 1,000 persons. However, the 7 year cumulative incidence of RDR was highest in those with a high HbA_{1c} level and short duration of diabetes at 73 cases per 1,000 persons (Figure 6.4.13). The seven year cumulative incidence of RDR in those with a low HbA_{1c} level with a short duration of diabetes was 13 cases (95% CI 10.2, 15.8) and 16 cases (95% CI 13.4, 18.6) with a long duration of diabetes. This increased to 73 cases (95% CI 68.9, 77.1) in those with a high HbA_{1c} and short duration of diabetes and 57 cases (95% CI 51.1, 62.9) with a high HbA_{1c} and long duration of diabetes. This lower incidence of RDR in those with a high HbA_{1c} and long duration of diabetes, compared to those with a short duration of diabetes may again be due to small numbers.

The one and two year cumulative incidence of RDR in those with a low HbA_{1c} level with a short duration of diabetes was 0 and 13 cases (95% CI 12.6, 13.4) and in those with a long duration of diabetes 0 and 16 cases (95% CI 15.4, 16.6). In those with a high HbA_{1c}, the one and two year cumulative incidence of RDR was 0 and 4 cases (95% CI 3.97, 4.03) with a short duration of diabetes and 7 (95% CI 6.9, 7.1) and 15 cases (95% CI 14.8, 15.2) with a long duration. Therefore, those with a low HbA_{1c} irrespective of duration of diabetes could be screened once every two years. Those with a high HbA_{1c} and a short duration of diabetes could be screened once every three years; and those with a high HbA_{1c} level and long duration of diabetes should undergo annual screening with the possibly of once every two years.

Figure 6.4.13: Cumulative incidence of RDR by HbA_{1c} at first screening and duration of diabetes in persons with T1DM



	Category	Total n	RDR cases n	*1 year	*2 years	*3 years	*4 years	*5 years	*6 years	*7 years
—	≤7% ≤10 years	93	1	0	13	13	13	13	13	13
—	>7% ≤10 years	310	11	0	4	13	24	38	60	73
....	≤7% >10 years	63	1	0	16	16	16	16	16	16
....	>7% >10 years	143	6	7	15	33	43	43	57	57

*Incidence is cases per 1,000 persons

6.4.2.4 Summary of main findings for persons with T1DM

- Nobody with T1DM with no evidence of DR at baseline developed PDR during the seven year study period.
- The seven year cumulative incidence (cases per 1,000 persons) of any DR, BDR and RDR was 536, 511 and 50 cases respectively.
- Duration of diabetes, glycaemic control, ethnicity and the presence of hypertension were significantly associated with a higher incidence of any DR, BDR and RDR after adjustment for age at diagnosis and gender.
- If screening intervals were stratified based on:

Ethnicity and glycaemic control then:

- Both Caucasians and non-Caucasians could be screened once every two years, irrespective of glycaemic control.

Ethnicity and duration of diabetes then:

- Caucasians with a short duration of diabetes could be screened once every three years.
- Caucasians with a long duration of diabetes could be screened once every two years.
- Non-Caucasians, irrespective of duration of diabetes could be screened once every two years.

Glycaemic control and duration of diabetes then:

- Low HbA_{1c}, irrespective of duration of diabetes, could be screened once every two years.
- High HbA_{1c} and a short duration of diabetes could be screened once every three years.
- Long duration of diabetes and high HbA_{1c} continue annual screening with the possibly of once every two years.

- However these findings should be interpreted with caution due to the small sample size and high dropout rate.

6.5 Discussion

The one year incidence of any DR, BDR and RDR in persons with T2DM or T1DM attending the CDE in Johannesburg, South Africa was relatively low at 18, 17 and 1 cases per 1,000 persons respectively in persons with T2DM and 28, 18 and 2 cases per 1,000 persons respectively in persons with T1DM. However, the seven year cumulative incidence of any DR and BDR in persons with T2DM was 351 and 331 cases per 1,000 persons respectively. Whilst in persons with T1DM the seven year cumulative incidence of any DR and BDR was higher at 536 and 517 cases per 1,000 persons respectively. Over the study period, the one year incidence of RDR increased for T2DM from 1 case per 1,000 persons to a seven year cumulative incidence of 47 cases and in T1DM from 2 cases per 1,000 persons to 50 cases per 1,000 persons respectively. The higher incidence of all levels of DR seen in persons with T1DM compared to those with T2DM may be due to differences in the population characteristics e.g. those with T1DM were younger, had a longer duration of diabetes and a higher HbA_{1c} level compared to persons with T2DM at first screening.

To date, no previous studies have reported on the incidence of DR in the African region including South Africa and only one study has reported incidence rates in Mauritius.(Tapp et al. 2006) This study reported the six year cumulative incidence rates in a multi-ethnic population of persons with T2DM based on retinal photographs of one eye only. The six year cumulative incidence of any DR was

23.8% and PDR was 0.4%. These incidence rates may be underestimated as retinal photography was restricted to one eye only, which may also result in some sight-threatening lesions being missed. However, the incidence of any DR was similar to what was seen in our study of 268 cases per 1,000 persons (26.8%).

The incidence of any DR, BDR and RDR was higher in non-Caucasians compared to Caucasians in our study in Johannesburg. Based on multivariate survival analysis after adjusting for confounding factors, non-Caucasians had a greater risk for incident DR in T1DM only. To date the incidence rates of DR worldwide have mainly been reported in Caucasian populations and the influence of ethnicity has only been looked at in relatively few studies. One study in America noted that black persons with T2DM were more likely to develop DR over a four year period than white persons (50% vs. 19% $p=0.002$), and even after adjusting for all other risk factors (glycaemic control, systolic blood pressure, type of diabetes treatment and gender) black persons were still at an increased risk compared to whites (OR 2.96 95% CI 1.00-8.78). (Harris et al. 1999) In a population of T1DM, the four year incidence of any DR was similar at 51% in African Americans and Caucasians, however, when controlling for other known risk factors, (time between examinations, glycaemic control, serum creatinine and duration of diabetes) African Americans had a lower risk of both development and progression of DR than Caucasians (both OR 2.62). (Arfken et al. 1994) The authors were not able to explore the reason for this lower risk. Whether these differences represent a genetic predisposition to microvascular damage remains unknown.

Increased HbA_{1c} level at baseline in our study was independently associated with the incidence of DR in both persons with T2DM and T1DM. Glycaemic control has

similarly been found in other studies to be strongly associated with both the development and progression of DR. The WESDR study found that each successively higher quartile of glycosolated haemoglobin at baseline, in both older and younger onset groups, was associated with an increasing incidence of DR.(Klein et al. 1994) The DCCT found in T1DM that intensive treatment reduced the incidence of DR by 76% and the progression of DR by 54%. They also discovered a residual protective effect on DR of this early tight control.(The Diabetes Control and Complications Trial Research Group 1993) A much lower (17%) risk of progression of DR was seen in the UKPDS for intensive glycaemic control in newly diagnosed persons with T2DM.(UK Prospective diabetes study group 1998b) However, in the DCCT there were also 10% of persons with good glycaemic control who developed DR (mean HbA_{1c} ≤6.9%) additionally 40% of those with poor metabolic control remained without evidence of DR (mean HbA_{1c} ≥9.5%).(Zhang et al. 2001)

In my study, increasing the duration of diabetes had the strongest association with the incidence of any DR, BDR and RDR after adjusting for age at diagnosis of diabetes, gender, ethnicity, HbA_{1c} and hypertension in both T2DM and T1DM. In persons with T2DM, the risk of developing RDR was 2.9 fold greater in those with a known duration of 5-10 years, with the risk essentially similar at 2.4 fold in those with a known duration of diabetes of >10 years compared to those with a known duration of <5 years. This unexpected finding may be a consequence of small numbers of persons developing RDR. The risk of developing RDR was 3.6 fold and 4.6 fold greater in persons with T1DM duration of 6-11 years and ≥12 years respectively compared to those with a duration of diabetes of ≤5 years. Similar findings have been reported in many studies as discussed in chapters 3-5.

In our study the presence of hypertension was also found to be associated with the development of DR but only in persons with T1DM. This was also the case in the WESDR study where diastolic blood pressure was a significant predictor of the progression of DR and the incidence of PDR in persons with younger onset diabetes,(Klein et al. 1998) but no association was seen for persons with older onset diabetes.(Klein et al. 1995) In the ACCORD study, there was also no beneficial effect of intensive versus conventional anti-hypertensive treatment, nor in the ABCD trial comparing moderate with tight blood pressure control, on the progression of DR in persons with T2DM.(Estacio et al. 2000, ACCORD study group et al. 2010) In contrast, the UKPDS found in persons with T2DM that for each 10mm Hg decrease in mean systolic blood pressure there was a 13% reduction in for microvascular endpoints. (UK prospective diabetes study group et al. 2000) The effects of blood pressure lowering treatments such as ACE inhibitors and β -blockers have found reductions in the risk of progression of retinopathy of 50% in persons with T1DM over 2 years (Chaturvedi et al. 1998) and 34% in persons with T2DM over 7 years.(UK Prospective diabetes study group 1998a) These effects were seen even after adjustment for glycaemic control. Therefore, there may be a threshold for blood pressure below which no additional benefit on the progression of DR can be seen. Unfortunately the systolic and diastolic blood pressure measurements were not available for assessment in our study as only the presence or absence of hypertension was available.

There was no association seen between total cholesterol levels and the incidence of any DR, BDR and RDR in our study with respect T1DM or T2DM. Unfortunately a large number of values for total cholesterol were missing which may account for this finding and therefore this was not retained within the adjusted Cox regression

models. The effect of cholesterol lowering has been investigated by studies previously with mixed results. Two trials have found positive associations between serum lipids and DR (Chew et al. 1996) or maculopathy,(Klein et al. 1991) with other studies finding beneficial effects of fibrates on hard exudates and macular oedema.(Harrold et al. 1969, Dorne 1977, Rencova et al. 1992, Freyberger et al. 1994, Keech et al. 2007, ACCORD study group et al. 2010, Morgan et al. 2013) This reduction in the onset of DR did not appear to be attributable to the lipid lowering effects of fibrates. Other non-lipid-related mechanisms that may explain the effect of fibrates on DR are the anti-inflammatory and antioxidant properties of fibrates.(Poynter et al. 1998, Delerive et al. 1999) However other studies have found no association.(Duncan et al. 1968, Sjolie et al. 1997, Colhoun et al. 2004, Thomason et al. 2004)

In our study there was a low one and two year cumulative incidence of RDR for persons with either T2DM or T1DM who had no evidence of DR at first screening event. Therefore, extending the screening interval in this population from annual to biennial in persons with T2DM would mean 1 case, and in T1DM 2 cases would be at risk of a delay in the detection of RDR. If the interval was extended to triennial this would increase to 5 and 7 cases in persons with T2DM and T1DM respectively. This is a similar risk to that seen in the DRSSW population (chapter 4). Both of these studies add to the increasing body of evidence which suggests that it would be safe to increase the screening interval beyond annual screening to biennial in those persons with T1DM or T2DM who had screened negative for DR.(Younis et al. 2003a, Younis et al. 2003b, Olafsdottir et al. 2007, Agardh et al. 2011, Aspelund et al. 2011, Jones et al. 2012, Looker et al. 2013, Porta et al. 2013, Stratton et al. 2013)

The multivariate analysis conducted demonstrated that the incidence of RDR was not uniform across the range of persons with diabetes and that certain subgroups may be at a higher or lower risk of DR. Due to the strong association between HbA_{1c}, duration of diabetes and the effects of ethnicity on the incidence of DR shown in this study in South Africa, these risk factors were used to further assess the cumulative incidence of DR. The various subgroup analyses demonstrated that persons with T2DM with good glycaemic control (HbA_{1c} ≤7.0%), and with T1DM of Caucasian origin with a duration of diabetes of 10 years or less could be safely screened beyond annual to once every two years or even three years. The increased incidence of RDR seen in non-Caucasians especially those with T1DM indicates that the screening interval should not be extended beyond once every two years. However, the numbers within the groups were small and therefore caution should be applied when interpreting these findings and recommendations. This is evidenced by some unexpected findings in the T1DM population of non-Caucasian origin with an HbA_{1c} level >7.0% having a lower 2 year cumulative incidence of RDR compare to those with an HbA_{1c} level ≤7.0%. Also those with an HbA_{1c} level >7.0% and a duration of diabetes of >10 years had a higher incidence of RDR until 5 years after a negative screening event at which point those with a duration of diabetes of <10 years had a higher incidence of RDR.

Almost all of the current evidence regarding optimal screening intervals based on data collected by DR screening programmes strongly suggest that it would be safe to extend screening intervals to at least biennial in persons without DR at first screening.(Younis et al. 2003a, Younis et al. 2003b, Olafsdottir et al. 2007, Misra et al. 2009, Agardh et al. 2011, Aspelund et al. 2011, Jones et al. 2012, Thomas et al.

2012, Four Nations Study Group 2013, Looker et al. 2013, Porta et al. 2013, Stratton et al. 2013) Two European screening programmes have assessed the effect of extending the screening interval from annual to biennial in Iceland and triennial in Sweden in persons with T2DM without previous evidence of DR within their respective programmes.(Olafsdottir et al. 2007, Agardh et al. 2011) In Iceland biennial screening intervals has been adopted as over a 10 year period of observation no patients without prior DR developed RDR. Annual screening was conducted following the detection of BDR.(Olafsdottir et al. 2007). In the Swedish programme a total of only three people developed maculopathy after three years of which only one person required laser therapy and none developed PDR.(Agardh et al. 2011). The latest evidence from the UK, i.e. the four nations diabetic retinopathy screening intervals project study group report has also suggested the possibility of an extension of the screening interval in persons without evidence of DR in both eyes at two consecutive annual screening events to once every two or three years.(Four Nations Study Group 2013)

Screening for DR although shown to be cost-effective is still expensive. Any cost-effectiveness savings made from re-organising screening programmes without an appreciably increased risk to patients are required especially in the current financial climate. An increase in the screening interval from annual to biennial has been estimated to achieve a 25% reduction in costs.(Chalk et al. 2012) However, individualising the screening interval based on a person's constellation of risk factors could further improve the cost effectiveness of screening. This allows screening to be conducted according to risk, avoiding unnecessary screening in the majority and possibly increased screening in those at risk resulting in less screening for the majority affording the possibility of more frequent screening in those at greatest risk.

The limitations of this study in Johannesburg, were previously stated in chapter 5, i.e. not representative of the majority of people in South Africa with diabetes, lack of dilation, and capture of only one macular centre 45° retinal image per eye, a high dropout rate of 31.4% (1,224) of persons who did not attend a second screening event despite being eligible. We unfortunately were not able to obtain information on those persons who did not participate in a second screening event. In addition to these using the Cox proportional hazards regression analysis instead of more sensitive parametric models such as Weibull (Akaike H 1974) may also be a limiting factor for the interpretation of the findings obtained in this study. In addition there is the issue of the small sample size especially for those with T1DM and those of non-Caucasian ethnicity which means some of the findings need to be interpreted with caution. The addition of other putative risk factors such as HbA_{1c}, ethnicity and the presence of hypertension, estimation of ACR, cholesterol levels and smoking habit were of added value in this study in addressing the risk of development of DR.

6.5.1 Summary of main findings

- The seven year cumulative incidence of any DR, BDR and RDR were lower in persons with T2DM compared to those with T1DM.
- After adjusting for confounders the incidence of any DR, BDR and RDR was associated with duration of diabetes, glycaemic control in T2DM with the addition of ethnicity and hypertension in persons with T1DM.
- The screening interval could be safely extended from annual to biennial in persons with both T2DM and T1DM where there is no evidence of DR at screening.
- There is also the possibility of extending the screening interval to triennial in persons with T2DM under good glycaemic control (HbA_{1c} ≤7.0%), and in

persons with T1DM, of Caucasian ethnicity and a short duration of diabetes (≤ 10 years) with no prior DR. However, due to the small study population, the low rate of RDR development and the dropout rate these findings should be interpreted with caution.

Chapter 7

Concluding Remarks

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7.1 General discussion

This thesis set out to describe the epidemiology of DR in persons with diabetes both T2DM and T1DM, attending the community based National DR Screening Service for Wales, (DRSSW) during the period of 2005-2009 and the Centre for Diabetes and Endocrinology in Johannesburg, South Africa. The reported prevalence and incidence of DR has varied considerably between the many different population groups studied globally, dependent on the type, according to differing classifications, and duration of diabetes, methods of detection and characteristics of the population studied. (Bodansky et al. 1982, Klein et al. 1985, Kristinsson et al. 1994a, Kristinsson et al. 1994b, Younis et al. 2002, Younis et al. 2003b, Younis et al. 2003a, Misra et al. 2009, Jones et al. 2012, Yau et al. 2012, Stratton et al. 2013)

This thesis determined the prevalence and incidence of DR in persons with diabetes over the age of 12 years in the above populations and also explored the risk factors associated with the development of DR over a period of four to 7 years respectively in those without evidence of DR at initial screening. However, due to the number of people who did not attend for further screening the incidence rates beyond 3 years should be interpreted with caution. The incidence of DR and the associated risk factors were then utilised to assess a safe screening interval based on a limited number of risk factors which included type of diabetes, duration of diabetes and treatment modality for those with T2DM from Wales and a more expansive risk profile including glycaemic control, the presence of hypertension, dyslipidaemia and ethnicity, for the population from Johannesburg. In addition visual acuity was assessed in both populations as it forms part of the screening process.

As mentioned above the prevalence and incidence of DR in a population of persons with diabetes living in Wales was derived from the National DR Screening Service in Wales, (DRSSW) UK which during 2005 and 2009 screened a total of 135,152

persons. The service employs standardised and quality assured protocols for image capture and grading. Following the assessment of visual acuity, digital retinal images were captured (2x45°) using Canon Dgi non-mydratic cameras. Image grading was then conducted by trained and accredited retinal graders utilising an enriched version of the UK national screening protocol. Quality assurance was undertaken on a monthly basis.

The prevalence and incidence of DR has not previously been estimated in such a large community based population undergoing routine annual retinal screening with standardised quality assured protocols for image capture and grading and therefore this dataset represents an unique opportunity to ascertain the prevalence of DR in the defined population and the development of DR over a period of four years in those with no DR at a single initial screening event. Based on the development of RDR over the study period it was estimated if the screening interval could be extended beyond the current annual screening.

91,393 (67.2%) of the 135,152 persons screened by the DRSSW between 2005 and 2009 were included for analysis. Reasons for excluding 43,759 (32.4%) were T2DM with an age at diagnosis of <30 years and T1DM with an age at diagnosis of ≥30 years (without confirmation from the patients GP). Of the 91,393 included 86,390 (94.5%) had T2DM and 5,003 (5.5%) had T1DM. The overall prevalence of any DR was 32.3%, BDR 27.3% and RDR 5.0%. The prevalence of any DR within the DRSSW population was lower in persons with T2DM compared to T1DM at 31.0% and 56.2% respectively. The majority of DR was BDR at 26.6% and 39.8% in T2DM and T1DM respectively with 4.4% and 16.4% respectively having RDR. The prevalence of any DR (31.0%) in persons with T2DM was similar to that

previously reported in other UK screening services using digital images both in Liverpool at 25.3% (Younis et al. 2002) and Norwich at 25.3% (Misra et al. 2009). A recent worldwide systematic review of studies involving retinal photography reported a similar prevalence at 25.2%. (Yau et al. 2012) In this study the prevalence of any DR (56.2%) in persons with T1DM was slightly higher than that reported earlier by Younis et al at 45.7%. (Younis et al. 2002) both being considerably lower than that reported in the global review at 77.3% (Yau et al. 2012) The Liverpool study observed slightly higher prevalence of RDR in T2DM compared to my findings at 6.0% vs. 4.0% respectively, although it was the same in persons with T1DM at 16.4%. (Younis et al. 2002) The prevalence of RDR that I observed in both T2DM and T1DM was much lower than that reported in the global review at 6.9% and 38.5% respectively. (Yau et al. 2012)

The cumulative incidence of DR within the DRSSW over the four year study period in persons with T2DM was 44.5% (445 cases per 1,000 persons) with any DR, 43.8% (438 cases per 1,000 persons) of BDR and 1.6% (16 cases per 1,000 persons) of RDR the annual incidence was higher in persons with T1DM at 64.9% (649 cases per 1,000 persons), 63.5% (635 cases per 1,000 persons) and 5.6% (56 cases per 1,000 persons), respectively. Interestingly 50% of those with T1DM who developed RDR had maculopathy without co-existing PPDR or PDR. Similarly, 56.6% of persons with T2DM who developed RDR also had maculopathy without co-existing PPDR or PDR. Only 6.8% of those with T1DM who developed RDR had PDR and 8.1% had PDR in T2DM. The four year cumulative incidence of RDR in persons with T2DM was lower in our study at 1.6% compared to the four year incidence of sight-threatening DR observed in the Liverpool DR screening programme at 2.1% (21 cases per 1,000 persons) (Younis et al. 2003a) and the five year cumulative incidence of RDR in the Norwich screening programme at 5.3% (53

cases per 1,000 persons).(Jones et al. 2012) However, in T1DM the incidence of sight-threatening DR in Liverpool was lower at 3.2% (32 cases per 1,000 persons) compared to the incidence of RDR seen in my study at 5.6%.(Younis et al. 2003b) Possible reasons for these differences include the different statistical methods used to calculate incidence rates, as well as differences between our classification of RDR and sight-threatening DR plus possible differences in population demography.

In this study there were no cases of RDR in persons with T2DM at the end of the first year following a single negative screening event. The two year incidence of RDR in persons with T2DM was 0.3% (3 cases per 1,000 persons). Therefore, the annual screening interval could safely be extended to once every two years for persons with T2DM without DR at their initial screening event. If the annual screening interval was further extended to once every three years 150 out of ~50,000 (0.3%) people, without evidence of DR at first screening would have had a delayed diagnosis of RDR. In comparison, the one year cumulative incidence of RDR in persons with T1DM was 0.1% (1 case per 1,000 persons) and at two years was 0.9% (9 cases per 1,000 persons). Therefore, if the screening interval was extended to once every two years then 2 people out of ~2,000 would have had a delayed diagnosis of RDR and if extended to once every three years then this would have increased to 18 people.

It was then considered that a safe screening interval maybe better defined if putative risk factors for the development of DR were employed to estimate the risk of developing RDR. In this study the increased duration of diabetes was independently associated with increased prevalence and incidence of any DR, BDR and RDR for both T2DM and T1DM. Similarly almost all DR epidemiological type

studies have found duration of diabetes to have a strong association with DR.(Younis et al. 2003a, Tapp et al. 2006, Cikamantana et al. 2007, Varma et al. 2007, Zhang et al. 2011) We also observed that insulin treatment in T2DM was significantly associated with the prevalence and incidence of any DR, BDR and RDR as has been shown in previous studies (Younis et al. 2003a, Jones et al. 2012). Studies involving the initiation of insulin therapy in T2DM (Roysarkar et al. 1993, Henricsson et al. 1995, Chantelau et al. 1997, Henricsson et al. 1997) have recorded a rapid progression of DR in poorly controlled persons. The association with insulin therapy could also be a reflexion of long term poor glycaemic control necessitating the use of insulin, with the possibility of an additional impact resulting from a rapid reduction in glucose levels especially in those with the poorest control.(Zhao et al. 2014)

The positive association of duration of diabetes in both T2DM and T1DM and type of treatment of diabetes in T2DM with the incidence of DR allowed us to examine further the impact of different risk stratification strategies. There were no cases of RDR with T2DM within the first year following a negative screening event. The two year incidence in those with T2DM treated with either diet alone, OHAs or insulin with a duration of diabetes of <5 years was 0.3% (3 cases per 1,000 persons) for both diet and OHAs and 0.1% (1 case per 1,000 persons) using insulin therapy. In those with a duration of diabetes of 5-9 years the two year incidence of RDR was 0.2% (2 cases per 1,000 persons) in those treated through diet alone, 0.4% (4 cases per 1,000 persons) in those on OHAs and 0.3% (3 cases per 1,000 persons) in those using insulin. Once the duration of diabetes was ≥ 10 years the two year incidence of RDR was 0.1% (1 case per 1,000 persons) for those on diet only, 0.3% (3 cases per 1,000 persons) in those taking OHAs and 1.1% (11 cases per 1,000 persons) for those requiring the addition of insulin. Therefore, the screening interval

could be extended to once every two years for those with T2DM and once every three years in those on diet only or using OHAs with a known duration of diabetes <10 years.

In persons with T1DM with a duration of diabetes of ≤ 10 years the incidence of RDR one year following a negative screening event was 0.1% (1 case per 1,000 persons) increasing to 0.5% (5 cases per 1,000 persons) after 2 years. Interestingly, those with T1DM for 11-19 years duration there were no cases of RDR one year after a negative screening, however there were 1.9% (19 cases per 1,000 persons) after two years. For those with T1DM for ≥ 20 years duration again there were no cases of RDR within the first year however, 2 years after there were 2.7% (27 cases of RDR per 1,000 persons). Therefore, all persons with T1DM should be screened at least once every two years especially those with a duration of diabetes in excess of 10 years and treated with either OHAs and/or insulin. If the duration of T1DM was ≤ 10 years then the screening interval could be further extended.

The main question to answer when trying to assess the optimal screening intervals is what amount of interval disease (number of people at risk of a delayed diagnosis of RDR) is acceptable and this will need to be balanced against the cost of screening and take into consideration the costs relating to visual impairment and blindness.(Looker et al. 2014) Other UK screening programmes have also recommended that screening intervals in those without DR could safely be extended beyond the current annual screening interval.(Younis et al. 2003b, Younis et al. 2003a, Jones et al. 2012, Looker et al. 2013, Stratton et al. 2013, Leese et al. 2015) The Liverpool screening programme calculated that the mean screening interval with a 95% probability of not missing sight-threatening DR was 5.4 years in persons

with T2DM and 5.7 years in those with T1DM.(Younis et al. 2003b, Younis et al. 2003a) However, they recognised the potential administrative difficulties and the risk of non-compliance with overly long screening intervals without a robust IT system support and therefore, recommended a screening interval of 2-3 years. The one and two year cumulative incidence of sight-threatening DR within the Liverpool screening programme was 0.3% and 0.8% in persons with T2DM and 0.3% and 0.8% in those with T1DM who would be at risk of a delayed diagnosis of sight-threatening DR.(Younis et al. 2003b, Younis et al. 2003a) In Norwich the annual incidence of RDR was calculated at <0.5% in persons with T2DM.(Jones et al. 2012) However, in Scotland it was estimated that in persons with 2 consecutive negative screening events the risk of progression to RDR within a 2 year screening interval was very low at $\leq 0.15\%$ in T2DM.(Looker et al. 2013) Most recently a report from the four Nations DR study group found that in persons with no evidence of DR in either eye at two consecutive screening events at least 12 months apart, between 0.3% and 1.3% progressed to RDR at 2 years with <0.3% requiring treatment..(Four Nations Study Group 2013, Leese et al. 2015) However, two important caveats within the report were; a robust IT system, in order to prevent the loss of patients from the service and ensuring accurate and consistent grading without with such a recommendation would be unsafe. This evidence is currently being considered by the UK national screening committee. Both of these caveats are met by the DRSSW with both a robust IT system and a quality assured call and recall system and grading. This study has also taken into consideration the impact of duration and type of diabetes in assessing risk of developing RDR.

In parallel my study explored the prevalence of visual impairment and blindness which were low at 6.6% and 0.4% in T2DM respectively and 2.8% and 0.1% respectively in T1DM. The limitation in interpreting this data is that it was either

attributable to DR or other conditions and it was not possible to distinguish between them as this information was not available then. The reason for the low prevalence of blindness within the DRSSW is likely due to the exclusion of persons who were registered blind as they would have difficulties following the screening procedures, or are under regular care of HES and therefore excluded from screening. No previous community based studies of screening programmes have reported the level of visual impairment and blindness in persons with T2DM and T1DM separately.

A second smaller dataset of persons with diabetes undergoing photographic based screening was provided from a diabetes management programme in Johannesburg, South Africa involving 5,515 persons screened between 2001 and 2010. This data promised an unique opportunity to further examine the epidemiology of DR in a different population with the additional information on more putative risk factors than were available to us in Wales at the time this analysis, such as glycaemic control, the presence of hypertension and dyslipidaemia. As part of its diabetes management programme at the Centre for Diabetes and Endocrinology (CDE), Johannesburg, South Africa, offers annual screening based on one macula centred retinal image taken through undilated pupils using the Canon CR6 non-mydratic camera following the assessment of visual acuity . Images were graded by a local diabetologist according to a standard DR grading protocol. However, due to differences between the grading protocol and that used in the DRSSW all images having DR were re-graded according to the DRSSW grading protocol by one of three trained retinal graders employed by the DRSSW. Despite the availability of more putative risk factors for this population the study was limited, due to its relatively small population size and therefore, findings should be interpreted with caution.

In the cohort of patients enrolled at the CDE there were 3,978 persons with T2DM and 1,537 persons with T1DM who underwent screening between 2001 and 2009. The combined (T2DM and T1DM) prevalence of DR reported in this study was: any DR 25.9% and RDR 7.6%, which is lower than previously seen from community based studies in South Africa who observed a prevalence of 62.2% with any DR and 44.5% with RDR, (Mash et al. 2007) 32.3% and 8.9% respectively (Read et al. 2007), and 33.4% and 11.7% respectively. (Carmichael et al. 2005) This may be due to the differences in the ethnicity and socio-demographics of persons with diabetes cared for in the private and public health care sectors in South Africa. The prevalence of DR was lower in persons with T2DM compared with T1DM (20.5% in T2DM versus 36.9% in T1DM). The majority of DR was BDR at 14.1% with 6.4% RDR in T2DM and 27.2% and 9.7% respectively in T1DM.

The seven year cumulative incidence of DR was 35.1% (351 case per 1,000 persons), 33.1% (331 cases per 1,000 persons) and 4.7% (47 cases per 1,000 persons) for T2DM and 53.6% (536 cases per 1,000 persons), 51.1% (511 cases per 1,000 persons) and 5.0 (50 cases per 1,000 persons) for T1DM. The one year cumulative incidence of RDR was low at 0.1% (1 case per 1,000 persons) with T2DM and 0.2% (2 cases per 1,000 persons) with T1DM. Therefore, if the annual screening interval was extended in the CDE then of the ~3,000 persons followed up without evidence of DR then 9 persons (3 with T2DM and 6 with T1DM) would have had a delayed diagnosis of RDR. Unfortunately none of the previous studies have reported the incidence rates of DR in Africa which limits any comparisons that could be made.

Increased HbA_{1c} and duration of diabetes were seen to be significantly associated with the prevalence and incidence of any DR, BDR and RDR in both T2DM and

T1DM. Similarly glycaemic control has been consistently found in other studies to be strongly associated with both the development and progression of DR.(The Diabetes Control and Complications Trial Research Group 1993, UK Prospective Diabetes Study group 1998a, b, Gaede et al. 2003, ACCORD study group et al. 2010) Some studies have also discovered a residual protective effect (legacy effect) on DR of early tight glycaemic control.(The Diabetes Control and Complications Trial Research Group 1993, Holman et al. 2008, White et al. 2010, Aiello et al. 2014) However, in the DCCT 10% of persons developed DR despite good metabolic control (mean HbA1c \leq 6.9%) and 40% of those with poor metabolic control remained without evidence of DR (mean HbA1c \geq 9.5%).(Zhang et al. 2001)

In the CDE population a non-Caucasian ethnicity was significantly associated with the prevalence of DR in both T2DM and T1DM but only associated with the incidence of DR in T1DM. To date on a worldwide basis the incidence rates of DR have mainly been reported for Caucasian populations, although two studies have reported higher incidence rates in African Americans with both T2DM and T1DM when compared to Caucasians.(West et al. 1982, Kalk et al. 1997) Whether these differences represent a genetic predisposition to microvascular damage and/or other risk factors remains unknown.

In the cohort from Johannesburg, South Africa the presence of hypertension was also found to be associated with the development of DR, but only in persons with T1DM. This was also seen in the WESDR study where diastolic blood pressure was a significant predictor for progression of DR and the incidence of proliferative DR in persons with younger onset diabetes,(Klein et al. 1998) but no association was seen in persons with older onset diabetes.(Klein et al. 1995) However, the

UKPDS and ABCD trials both demonstrated the importance of hypertension as a risk factor for micro- and macro-vascular complications in type 2 diabetes.

However, the more recent ACCORD and ADVANCE trials did not find a beneficial effect of lowering blood pressure on DR.(Beulens et al. 2009, ACCORD study group et al. 2010) A reason for the non-beneficial effect for lowering blood pressure on DR found in the ACCORD and ADVANCE trials compared with the UKPDS study may be due to much higher initial BP and greater reduction on treatment seen in the UKPDS study.

The risk factors found to be associated with the incidence of RDR within the CDE population i.e.; duration of diabetes and HbA_{1c} in both T2DM and T1DM and ethnicity and hypertension in T1DM were incorporated into risk analysis to determine the impact of different screening stratifications. Due to the small population size the analyses had to be conducted for a combination of two risk factors. For persons with T2DM this was HbA_{1c} and duration of diabetes and for T1DM these were: ethnicity and HbA_{1c}, ethnicity and duration of diabetes and HbA_{1c} with duration of diabetes. In persons with T2DM and an HbA_{1c} ≤7.0% and a known duration of diabetes ≤10 years the incidence of RDR one year after a negative screening was 0.2% (2 cases per 1,000 persons) rising to 0.4% (4 cases per 1,000 persons) 2 years after a negative screen (Table 7.1). Surprisingly once the known duration of diabetes increased to >10 years there were no cases of RDR one or two year after a negative screen. For those with an HbA_{1c} >7.0% and a duration of diabetes ≤10 years the one year incidence of RDR was 0.1% (1 case per 1,000 persons) increasing to 0.7% (7 cases per 1,000 persons) after 2 years. Once the known duration of diabetes had increased to >10 years there were no cases of RDR on year following a negative screening event however two years after this was 0.9% (9 cases per 1,000 persons) Therefore, those persons with an HbA_{1c} of ≤7.0%

regardless of known duration could undergo screening once every three years whilst those with an HbA_{1c} of >7.0% would need to be screened once every two years.

Table 7.1: The one and two year incidence of RDR in persons with T2DM

	Duration of diabetes	
	≤10 years	>10 years
HbA _{1c}	≤7.0%	1 year 2 cases 2 years 4 cases
	>7.0%	1 year 1 case 2 years 7 cases
		1 year 0 cases 2 years 0 cases
		1 year 0 cases 2 years 9 cases

Incidence is cases per 1,000 persons

For persons with T1DM the one and two year incidence of RDR is shown in Table 7.2. For Caucasians the one and two year incidence of RDR was 0% and 0.7% (7 cases per 1,000 persons) with an HbA_{1c} ≤7.0% and 0.3% and 0.6% (3 and 6 cases per 1,000 person) respectively with an HbA_{1c} >7.0%. For non-Caucasians the one and two year incidence of RDR was 0 and 4.0% (40 cases per 1,000 persons) respectively with an HbA_{1c} ≤7.0% and 0.7% and 1.5% (7 and 15 cases per 1,000 persons) respectively with an HbA_{1c} >7.0%. In Caucasians with a duration of diabetes ≤10 years the incidence of RDR one and two years after a negative screening event was 0 and 0.3% (3 cases per 1,000 persons) respectively and with a duration of diabetes >10 years was 0.5% and 1.1% (5 and 11 cases per 1,000 persons) respectively. In non-Caucasians with a duration of diabetes ≤10 years the one and two year incidence of RDR was 0 and 1.5% (15 cases per 1,000 persons) respectively and with a duration of diabetes >10 years was 0 and 5.6% (56 cases per 1,000 persons) respectively. Excluding ethnicity from the stratification in those with an HbA_{1c} ≤7.0% the one and two year incidence of RDR was 0 and 1.3% (13 cases per 1,000 persons) respectively and in those with a duration of diabetes ≤10

years and 0 and 1.6% (16 cases per 1,000 persons) respectively with a duration of diabetes >10 years. Once HbA_{1c} was >7.0 the one and two year incidence of RDR was 0 and 0.4% (4 cases per 1,000 persons) respectively with a duration of ≤10 years and 0.7% and 1.5% (7 and 15 cases per 1,000 persons) respectively with a duration of >10 years. Therefore those persons of Caucasian ethnicity with a duration of diabetes ≤10 years the two year incidence of RDR was sufficiently low (0.3%) to allow an extension of the screening interval to once every three years. With the exception of non-Caucasians with an HbA_{1c} >7.0% or Caucasians with a duration of diabetes of >10 years or an HbA_{1c} >7.0% and a duration of diabetes >10 years whose one year incidence of RDR was sufficiently high to recommend maintaining annual screening intervals all other groups could undergo screening once every two years. However this analysis should be interpreted with caution as the population size was small and further larger scale studies are required before the screening interval can safely be modified. In addition those persons enrolled in the CDE cannot be regarded as representative of the majority of the population of persons with diabetes in South Africa.

Table 7.2: One and Two year incidence of RDR in persons with T1DM by ethnicity and HbA_{1c}, ethnicity and duration of diabetes and duration of diabetes and HbA_{1c}

	Ethnicity	
	Caucasian	Non Caucasian
HbA _{1c}	≤7.0%	1 year 0 cases 2 years 7 cases
	>7.0%	1 year 3 cases 2 years 6 cases
Duration	≤10 years	1 year 0 cases 2 years 3 cases
	>10 years	1 year 5 cases 2 years 11 cases
Duration	≤10 years	1 year 0 cases 2 years 13 cases
	>10 years	1 year 0 cases 2 years 16 cases

Incidence is cases per 1,000 persons

The prevalence of visual impairment and blindness were low in this cohort of persons with diabetes at 3.5% and 0.3% respectively for persons with T2DM and 1.8% and 0.2% respectively for those with T1DM. The prevalence of visual impairment and blindness in populations in South Africa have not previously been reported.

This study shows that information on additional putative risk factors for the development of DR could be useful in better ensuring the safety of extended screening intervals. In the future it may be beneficial to consider individualising the screening interval based on the level of DR observed together with the available risk

factors. A study in Demark developed an algorithm to calculate a persons' screening interval based on the presence of retinopathy, type of diabetes, duration of diabetes, HbA_{1c}, systolic blood pressure and gender.(Aspelund et al. 2011) The study imposed a minimum screening interval of 6 months and maximum of 60 months. Using this approach they found the mean recommended screening interval to be 29 months. This corresponds to a 59% reduction in screening frequency compared to annual screening with 2.9% developing sight-threatening DR before the next screening visit. The algorithm was tested on a database containing 5,199 patients over a period of 20 years. This study showed that individualising the screening interval based on putative risk factor information could make screening more efficient. However, whether additional risk factors for DR such as treatment of diabetes and cholesterol levels would provide a more sensitive algorithm needs to be investigated. The main barrier to introducing such an algorithm in UK screening programmes is that they don't collect such information on the putative risk factors. Therefore, capturing this information possibly through improved IT links with GP's or Laboratories or collection at the point of screening, would need to be carefully considered before individual risk based screening could be introduced.

Due consideration should also be given to service user views / opinions before any adjustments to screening intervals are introduced. We have conducted two earlier studies exploring patient perceptions of extending beyond the current annual screening interval. One study involved a patient questionnaire which revealed that 85% of those who responded think that they should have their eyes screened every year. 65% stated that they would except an extended screening interval as long as medical evidence proved it was safe.(Yeo et al. 2012b) Therefore, If any changes are to be made in the future the concerns of those 35% who did not agree needs to be taken into consideration. The second study utilised a discrete choice experiment

in an attempt to understand the preferences of persons with diabetes for screening provisions. The findings were that although the frequency of screening was a valued attribute they would be willing to have the screening interval extended if other preferences for service provision, such as the ability to detect other changes in the eyes, were taken into account.(Yeo et al. 2012a)

Underprovided education/information about DR, resulting in a lack of awareness of the seriousness of the detrimental effects of DR on visual acuity, is cited to be one of the main barriers to attendance.(Van Eijk et al. 2012, Shepple et al. 2014) This coupled with the evidence that those persons who do not attend for screening are at 3.78 fold increased risk of developing RDR compared to those who do attend is of concern when considering extending screening intervals.(Leese G P et al. 2008) Therefore, a patient education/awareness programme should be implemented in conjunction with the planning allied to modifying the screening interval according to risk to ensure attendance. Additional measures to improve attendance should be investigated e.g. offering out-of-hour screening and weekends. In addition a text message reminder system could be implemented.

7.2 Study Limitations and Strengths

There were a number of limitations within this thesis for both study populations as there are for all retrospective observational studies especially when attempting to estimate the impact of changing the screening interval beyond annual screening. The DRSSW excluded persons under the care of ophthalmology, registered blind or under the age of 12 years from screening and therefore they could not be included in the analysis. Other exclusions were also made to ensure the quality of the data to be analysed within this thesis i.e. persons with T2DM with an age at diagnosis of

diabetes <30 years or T1DM with an age at diagnosis of ≥ 30 years. The main limitations of the DRSSW cohort were the number of exclusions and the limited number of risk factors available for analysis. In the South African cohort persons with a diagnosis of diabetes other than T2DM or T1DM were excluded. The main limitation of the South African dataset was the small sample size which limited the conclusions that could be drawn from the analysis. Also the population examined from South Africa was from a private healthcare sector of the population and therefore not representative of the majority of persons with diabetes in South Africa. The study dropout rate observed beyond the second screening event was also a limitation in both studies. In the T2DM population in DRSSW 38% did not undergo a third screening event, which increased to 79% for a fourth screening event. For the T1DM population 37% did not undergo a third screening event, increasing to 76% at the fourth screening event. In the South Africa study for the T2DM population the dropout rate at the third screening event was 35% increasing to 76% at the fourth screening event. For the T1DM population this was 29% and 49% respectively. The reasons for the dropouts could not be investigated, due to the anonymous nature of the data sets, could bias the findings. These limit the conclusions that can be drawn from these studies especially beyond the third screening event and in the South African dataset.

Another study limitation was that the best corrected visual acuity was not measured and current acuity was used instead. Although if the current visual acuity was lower than 6/9 a pinhole measurement was recorded. Additionally the visual impairment and blindness found within these studies could not be attributed to DR as recordings of other lesions were not present within the datasets.

A possible limitation of this study and its analysis was to rely on only one negative screening event on which to stratify screening intervals, however, the risk of developing RDR was similar to that described by the Four Nations diabetic retinopathy screening interval study group in those with no retinopathy detected at two screening episodes one year apart where the four year incidence of RDR ranged from 0.3% and 1.3% over the seven programmes included in the study

However, the strengths of this study were the large population size of the Welsh cohort and the utilisation of standardised screening methodologies employed to both capture and grade digital retinal images within each programme. Visual acuity was also recorded by trained healthcare assistants using 3m illuminated Snellen charts.. Grading was performed by accredited graders in a structured 3 tiered process using a modified version of the NSC grading protocol. In the CDE visual acuity and image capture was performed by diabetes nurses educators also using a 3m illuminated Snellen chart, but capturing only one macular centred image without mydriasis. Grading was performed initially by one local diabetologist using the CDE's standard grading protocol, although all images with DR lesions were re-graded by one of three (including myself) accredited graders according to the Welsh grading protocol. Those images with no DR were not included in the re-grading process. In addition was the availability of a greater number of risk factors.

7.3 Future Research

Future research should continue to focus on individualising screening intervals using more detailed risk factor analysis in a prospective study in order to define low, medium and high risk individuals and corresponding safe screening intervals. For this purpose it will be necessary to include the following putative risk factors: type of

diabetes (according to an agreed classification), duration of diabetes (accepting the difficulty with type 2 diabetes), blood pressure, lipid profile, ethnicity and concomitant medication. Standardised protocols for the acquisition of images and grading is essential along with quality assurance procedures as was adopted in this thesis. It is also essential to ensure a validated register of the population under study and well defined inclusion and exclusion criteria. A patient centred approach is a main future requirement. This could be achieved by a prospective randomised controlled trial to compare annual screening and risk-based screening intervals varying between 6 months for high risk individuals, 12-24 months for medium risk and 36 months for low risk individuals. This would need to be accompanied by cost-effectiveness analysis across the different screening intervals.

Further comparison between the need for one versus two successive annual screen negative episodes would be of additional value. Additionally screening intervals for persons with pre-existing BDR and possibly more advanced DR such as PPDR should be further investigated along with health economics.

Studies should also consider assessing the outcomes of those persons referred for DR to the HES. Consideration should be given to whether the referrals were appropriate, whether treatment was given and if so was it carried out in timely manner.

The impact of changing the screening intervals on the attitudes of patients towards DR screening should be carefully assessed. Qualitative Research needs to assess

how best to communicate these changes and the reasons behind them to the patients to ensure up take of screening remains unaffected.

Beyond screening intervals other ways to ensure the cost effectiveness of screening programmes for DR should be investigated such as improving the uptake rate for screening and the adoption of new or emerging technologies into screening programmes such as automated grading and the role of optical coherence tomography (OCT) for the detection of macular oedema which is difficult with the current 2-D images obtained with the non-mydratic cameras.

Additional research should also focus on the mechanisms involved in the development and progression of DR thereby developing better less destructive treatments such as the anti-VEGF treatments and other medications such as the fibrates.

7.4 Summary

The evidence emanating from my analysis in this thesis in conjunction with previous studies from diabetic retinopathy screening programmes in the UK,(Younis et al. 2003b, Younis et al. 2003a, Jones et al. 2012, Looker et al. 2013, Stratton et al. 2013, Leese et al. 2015) and in Europe (Olafsdottir et al. 2007, Agardh et al. 2011, Aspelund et al. 2011, Porta et al. 2013) provide an increasing evidence base for the extension of screening intervals in a low-risk population. Additional studies have also demonstrated that extending the screening interval would also be cost-effective with as much as a 25% reduction in the costs of screening.(Chalk et al. 2012)

The high prevalence of DR at entry into both of the programmes examined in this thesis emphasises the importance of such programmes in an attempt to eliminate the incidence of sight-threatening DR, in persons with diabetes. Progress has been made over the years with changes in diabetes care with earlier diagnosis, lower glycaemic, blood pressure and cholesterol targets lowering the prevalence of DR.(Vallance et al. 2008, Kyto et al. 2011) Other recent evidence shows that DR is for the first time no longer a leading cause of blindness in the working age population in England and Wales.(Liew et al. 2014) The authors suggested that this may in part be due to screening programmes for DR as well as improved diabetes care. However, more needs to be done to further reduce the incidence of blindness from DR through understanding its pathophysiology and development of new treatments in light of the ongoing global diabetes epidemic, with an estimated 387 million persons affected in 2014 which is expected to rise to 592 million persons with diabetes by 2035, especially in low or middle income countries (International Diabetes Federation 2014) with the accompanying risk of sight-threatening DR.

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Appendix 1 Thomas RL et al. Incidence of Diabetic Retinopathy in persons with Type 2 Diabetes Mellitus within a National Screening Programme – retrospective analysis. BMJ 2012; 344: e874

RESEARCH

Incidence of diabetic retinopathy in people with type 2 diabetes mellitus attending the Diabetic Retinopathy Screening Service for Wales: retrospective analysis

 OPEN ACCESS

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Abstract

Objectives To determine the incidence of any and referable diabetic retinopathy in people with type 2 diabetes mellitus attending an annual screening service for retinopathy and whose first screening episode indicated no evidence of retinopathy.

Design Retrospective four year analysis.

Setting Screenings at the community based Diabetic Retinopathy Screening Service for Wales, United Kingdom.

Participants 57 199 people with type 2 diabetes mellitus, who were diagnosed at age 30 years or older and who had no evidence of diabetic retinopathy at their first screening event between 2005 and 2009. 49 763 (87%) had at least one further screening event within the study period and were included in the analysis.

Main outcome measures Annual incidence and cumulative incidence after four years of any and referable diabetic retinopathy. Relations between available putative risk factors and the onset and progression of retinopathy.

Results Cumulative incidence of any and referable retinopathy at four years was 360.27 and 11.64 per 1000 people, respectively. From the first to fourth year, the annual incidence of any retinopathy fell from 124.94 to 66.59 per 1000 people, compared with referable retinopathy, which increased slightly from 2.02 to 3.54 per 1000 people. Incidence of referable retinopathy was independently associated with known duration of diabetes, age at diagnosis, and use of insulin treatment. For participants needing insulin treatment with a duration of diabetes of 10 years or more, cumulative incidence of referable retinopathy at one and four years was 9.61 and 30.99 per 1000 people, respectively.

Conclusions Our analysis supports the extension of the screening interval for people with type 2 diabetes mellitus beyond the currently

recommended 12 months, with the possible exception of those with diabetes duration of 10 years or more and on insulin treatment.

Introduction

Diabetic retinopathy remains a major cause of visual impairment and blindness in the United Kingdom,¹ with its early detection and timely treatment²⁻⁴ capable of reducing the risk of visual loss. The evidence that screening for diabetic retinopathy is cost effective^{5 6} has led to the establishment, over the past 20 years, of several screening programmes at local, regional, and national levels throughout the UK and elsewhere, varying in size, design, and complexity.^{7 8}

Various methods have been used to screen for diabetic retinopathy, including ophthalmoscopy (direct and indirect),⁹ obtaining retinal images (for example, Polaroid images),⁹⁻¹¹ 35 mm transparencies,¹² and more recently digital images with¹³ or without mydriasis;^{14 15} as well as combining ophthalmoscopy with retinal photography.^{16 17} In 1999, the National Screening Committee for England and Wales recommended the use of digital photography through dilated pupils to screen people for diabetic retinopathy^{18 19} from the age of 12 years. A national consensus protocol for grading and disease management, based on annual screening,²⁰ was also developed as part of the yearly review for every person with diabetes. In 2003, the Diabetic Retinopathy Screening Service for Wales was established and is currently responsible for the annual screening of 150 000 people registered with diabetes mellitus in Wales (about 5% of the population).

Despite the increase in diabetes mellitus worldwide,²¹ some evidence has suggested a decline during the past few decades in the prevalence and incidence of diabetic retinopathy,

especially sight threatening retinopathy. This reduction is attributed not only to improved care but also to the earlier detection of both diabetes and diabetic retinopathy.²²⁻²⁴ Evidence from screening programmes of relatively small numbers of patients with type 2 diabetes has also suggested that an extension of the screening interval—beyond the currently recommended 12 months—would be safe for those without evidence of retinopathy at first screening.²⁵⁻²⁹ Such a change in policy could substantially reduce health service expenditure while allowing reinvestment into the screening service. This reinvestment could provide more frequent screening for people with early exudative maculopathy and early diabetic retinopathy, and allow earlier discharge of patients at the hospital eye service as a result of more frequent follow-up being available at the screening service. Our study reviewed data for a large population of people with type 2 diabetes mellitus who had shown no evidence of diabetic retinopathy at their first screen. We estimated the annual and cumulative incidence of retinopathy over a four year period, and explored the association between the development of retinopathy and its putative risk factors.

Methods

Study population

Every person known to have diabetes mellitus over the age of 12 years and registered with a general practice in Wales must be referred to the Diabetic Retinopathy Screening Service for Wales by their doctor, apart from those excluded on medical grounds (for example, those unable to attend screening owing to infirmity or comorbidity)³⁰ or those already attending hospital based ophthalmology services because of retinopathy. Our four year retrospective analysis included data for all patients classified as having type 2 diabetes mellitus, diagnosed over the age of 30 years, and who attended screening between January 2005 and November 2009. Exclusion criteria included: a diagnosis, on referral to the screening service, of type 1 diabetes mellitus; a diagnosis of type 2 diabetes mellitus but at age younger than 30 years; or no type of diabetes mellitus recorded on the referral notification (predominantly from primary care). Data were anonymised before undergoing statistical analysis.

Screening procedure

After registration with the Diabetic Retinopathy Screening Service for Wales, each patient is invited to attend screening at a location closest to them (with an appointment date and time). Screening is undertaken at a variety of venues throughout Wales, including general practice surgeries and local hospitals or community centres. A trained healthcare assistant assesses patients' current visual acuity in both eyes (achieved with or without glasses or with pinhole reading), using an illuminated 3 m Snellen chart. Tropicamide (1%) is then applied to each eye, and after about 15 minutes, a trained photographer takes two 45° digital retinal images per eye (one macular centred, and one nasal field) using a non-mydratic Canon DGi camera (with a 30D or 40D camera back). The retinal images are transferred to a central reading centre for grading. The photographers can also take additional images of the retina, lens, or iris if deemed necessary.

Diabetic retinopathy grading

Trained staff use a standardised protocol to grade diabetic retinopathy, which is an enriched version of the English National Screening Protocol,²⁰ and take the worst grade for either eye as the final grading level. We used the following grading categories

of retinopathy: none present, background, preproliferative or proliferative, and maculopathy (based on surrogate markers such as exudates within 1 disc diameter of the fovea).

For the statistical analysis, we defined referable retinopathy as participants with preproliferative or proliferative retinopathy (with or without maculopathy), or maculopathy with background retinopathy. This category relates to those who would, according to guidelines, need referral to the hospital eye service for further assessment or treatment. Digital retinal images were not considered gradable if the retina of both eyes could not be visualised adequately—that is, retinal vessels were not visible within 1 disc diameter of the centre of the fovea and fine vessels were not visible across the surface of the optic disc.

Ethical approval

We sought advice from the South East Wales research ethics committee, as well as from the Cardiff and Vale University Health Board (previously the Cardiff and Vale National Health Service trust), the host organisation for the Diabetic Retinopathy Screening Service for Wales, on behalf of the Welsh Assembly Government. In their considered opinion, this study was a service evaluation and therefore did not require ethical approval. Individual patients provided written informed consent at each screening event for their anonymised data to be used in research.

Statistical analysis

We used descriptive analyses to characterise the study population and patterns of diabetic retinopathy, and used *t* tests and χ^2 tests to explore differences between patients without any retinopathy and those who developed any, background, or referable retinopathy. Parametric survival analysis with covariates identified those factors associated with the development of referable retinopathy.

The presence or absence of diabetic retinopathy was determined after each screening event during the study period. Although intended to occur annually, screening took place at variable times during the four year period. For people who developed retinopathy between two screening events, the time to development lay between the two episodes, and therefore the data were interval censored; for those who did not develop the disorder by the final screening event, the data were right censored. We therefore modelled the time to development of retinopathy using survival analysis to allow for these two types of censoring.

We used a parametric approach, implemented by the routine INTCENS program in Stata. From the estimated parameters, the survival function was calculated to derive the annual and cumulative incidence of any and referable diabetic retinopathy. We used bootstrapping to calculate confidence intervals, because we could not obtain the standard errors easily.³¹ Different distributions were considered for the underlying survival times, including Weibull, exponential, Gompertz, log normal, and inverse Gaussian. We chose the distribution on the basis of the Akaike information criterion.³²

We explored the effect of putative risk factors with available information (that is, age, sex, age at diagnosis, duration of diabetes mellitus, and treatment types) by incorporating them into this survival analysis. To avoid assumptions of linearity, we used the following categories for the duration of diabetes: less than five years, five to nine years, and 10 years or more. Age categories were: 30-49 years, 50-59 years, and 70 years or older. The risk factors were examined individually and then re-examined in a multivariate analysis with all variables included. We did statistical analyses using SPSS version 16 and

Stata version 10; evidence of significance was taken as $P < 0.05$ unless otherwise stated.

Results

A total of 85 214 individuals with type 2 diabetes mellitus underwent screening for diabetic retinopathy between January 2005 and November 2009; 57 199 (67.1%) had no evidence of retinopathy and were therefore eligible for inclusion in this study. At the initial screening event, 22 501 (26.4%) had evidence of background retinopathy and 3723 (4.4%) had referable retinopathy. Those with referable retinopathy consisted of: 1169 (1.4%) with maculopathy, 1279 (1.5%) preproliferative retinopathy, and 262 (0.3%) proliferative retinopathy (817 (1.0%) preproliferative retinopathy and maculopathy, 196 (0.2%) proliferative retinopathy and maculopathy). We excluded 1791 (2.1%) participants who had images that could not be graded, as well as those with evidence of existing retinopathy.

Of 57 199 people without evidence of diabetic retinopathy at the first screening event, 7436 (13.0%) did not attend another screening during the study period, 449 (6.0%) of whom were not eligible for a second screen (which would have occurred within 12 months). We do not know why the remaining 6987 (94.0%) people did not attend a second screening event, because anonymisation of the records prevented further investigation; however, this group was older and had a longer known duration of diabetes than the group attending at least one additional screening event (table 1). We did not observe a significant difference in the proportions of male participants between these two groups.

We found that 49 763 participants had a second screening event, 31 924 (64.2%) a third, 10 615 (21.3%) a fourth, and 767 (1.5%) a fifth (total of 93 069 events). Although screening was intended to occur annually, the screening intervals were generally longer than one year, with a mean (standard deviation) interval of 17.8 (6.3) months between the first and second screening events, 15.3 (4.4) months between the second and third, 13.2 (2.7) months between the third and fourth, and 12.0 (1.9) months between the fourth and fifth. Only 4479 (9%) participants had an interval of 12 (1) months between screening events.

During the study, 12 922 (26.0%) participants with type 2 diabetes mellitus developed diabetic retinopathy, of whom the vast majority (12 574 (97.3%)) developed background retinopathy. Of 348 (0.7%) people who developed referable retinopathy, 197 (56.6%) had evidence of maculopathy, 107 (30.7%) had preproliferative retinopathy, and 25 (7.2%) proliferative retinopathy. Sixteen (4.6%) people had preproliferative retinopathy and maculopathy, and three (0.9%) had proliferative retinopathy and maculopathy.

Of 28 participants who developed proliferative diabetic retinopathy (with or without maculopathy), 14 (50.0%) did so between 12 and 24 months after the first screening event, three (10.7%) after 24–36 months, 10 (35.7%) after 36–48 months, and one (3.6%) after 48 months. Duration of diabetes was less than five years in 19 (68%) participants, and 27 (96%) received diet and oral treatment, with only one receiving insulin. Of participants who developed proliferative retinopathy within 12 to 24 months, none were on insulin treatment and only two (14%) had had diabetes longer than 10 years.

In the survival analysis, we selected the Weibull distribution as best fitting the data. Tables 2 and 3 show the estimated annual and cumulative incidence of any and referable diabetic retinopathy. The annual incidence of any retinopathy at one year was 124.94 per 1000 people, decreasing to 66.59 per 1000 at four years, with a cumulative incidence of 360.27 per 1000

people at four years. By contrast, the annual incidence of referable retinopathy increased from 2.02 to 3.54 per 1000 people, with a cumulative incidence of 11.64 at four years. The cumulative incidence of each retinopathy group was about twice as high in participants who received insulin treatment (tables 2 and 3).

Table 4 summarises the baseline characteristics of the three groups according to outcome—that is, participants who did not develop diabetic retinopathy and those who developed any or referable retinopathy. The mean known duration of diabetes mellitus and the proportion of participants requiring insulin treatment were significantly greater in those who developed referable retinopathy than in those who remained free of retinopathy. Mean ages at diagnosis of diabetes and at first screening were lowest in the group that developed referable retinopathy and highest in the group that did not develop any retinopathy. Sex distribution did not differ between the groups.

Table 5 shows the effects of putative risk factors on the risk of participants developing diabetic retinopathy. A significantly raised risk of referable retinopathy was associated with an increased duration of diabetes mellitus. Risk was highest in participants diagnosed at age 30–49 years, with significantly reduced risks in those aged up to 70 years at diagnosis. The risk of any or referable retinopathy varied greatly between different types of diabetes treatment. Age, duration of diabetes, and treatment had similar effects on the risk of developing background retinopathy, although age at diagnosis of more than 70 years was associated with a significantly increased risk.

The incidence of referable retinopathy varied considerably between subgroups. For example, for participants given diet treatment only with a known duration of diabetes of less than five years, the cumulative incidence of retinopathy at one, two, and three years from the first negative screen was 1.83, 3.66, and 5.45 per 1000 people, respectively. Corresponding values for participants receiving insulin treatment with a duration of diabetes of less than 10 years were 0.71, 3.80, and 10.10 per 1000 people, respectively. For participants with a duration of diabetes of 10 years or more, the use of insulin treatment increased cumulative incidence greatly (with insulin treatment 2.24, 5.86, and 10.33 per 1000 people; without insulin treatment 9.61, 17.10, and 24.26 per 1000 people).

Discussion

In our study relating to people with type 2 diabetes mellitus enrolled in the national Diabetic Retinopathy Screening Service for Wales from 2005 to 2009 with no evidence of diabetic retinopathy at initial screening, the annual incidence of any retinopathy per 1000 people was 124.94 (12.5%) in the first year, falling each year to 66.59 (6.7%) in the fourth year. The cumulative incidence at four years was 360.27 per 1000 people (36.0%). The annual incidence of referable retinopathy per 1000 people was low at 2.02 (0.2%) in the first year, with a small increase to 3.54 (0.4%) in the fourth year; the cumulative incidence at four years was 11.64 (1.2%).

The incidence of referable retinopathy was positively and independently associated with the known duration of type 2 diabetes and the need for insulin treatment, and inversely related to age at diagnosis. For participants on diet treatment with a duration of diabetes of less than five years, the cumulative incidence of referable diabetic retinopathy at one, two, and three years was 1.83, 3.66, and 5.45 per 1000 people, respectively. By contrast, the corresponding values for participants using insulin treatment with a duration of diabetes of more than 10 years were 9.61, 17.10, and 24.26 per 1000 people, respectively,

an approximately fivefold increase. For participants not using insulin with a duration of diabetes of more than 10 years, the corresponding values were 2.24, 5.86, and 10.33 per 1000 people, respectively, and 0.71, 3.80, and 10.10 per 1000 people, respectively, for those using insulin treatment with a duration of diabetes of less than 10 years.

The results suggest that for people with type 2 diabetes mellitus and no evidence of retinopathy at screening, the interval of screening could be extended beyond the 12 months currently (but rarely) adopted. Patients on insulin treatment with a history of diabetes of 10 years or more should continue to be screened annually.

Strengths and weaknesses of the study

The large sample size was one of the main strengths of this study. Furthermore, all participants were screened for the presence of retinopathy by a standardised protocol of digital retinal imaging and subsequent grading by trained staff. However, screening was restricted to two 45° retinal images per eye, and only limited information was available on putative risk factors for the development of diabetic retinopathy (we could not obtain measures of glycaemic control, blood pressure, and lipid concentrations). We recorded a high dropout rate (12%) of participants who did not have a second screening event despite being eligible. We were not able to obtain information for those people who did not participate in screening; some may have been excluded for medical reasons, because they were already receiving care from an ophthalmologist for diabetic retinopathy, or they did not attend for other unknown reasons.

Comparison with other studies

The annual incidence of referable diabetic retinopathy observed in our study was similar to that previously reported by Younis and colleagues from the Liverpool Diabetic Eye screening programme for sight threatening retinopathy (equivalent to our category of referable retinopathy)—0.2% in the first year, with a cumulative incidence of 1.7% at four years.²⁶ The authors recommended an extension of the screening interval to triennial screening, based on the 95% probability of people remaining free from sight threatening retinopathy with a mean screening interval of 5.4 years.

Data from the annual screening programme in Norfolk²⁸ and the biennial screening programme in Iceland²⁵ also concluded that biennial screening intervals would be safe in those people without evidence of diabetic retinopathy at screening. The Icelandic screening programme reported that people who developed sight threatening retinopathy were placed on annual screening once they were identified as having background retinopathy. Therefore, these patients had no undue delay in the diagnosis or treatment of sight threatening retinopathy over the 10 year period of observation.²⁵

A study of the Swedish screening programme used a three year screening interval in a cohort of well controlled participants (mean HbA_{1c} 6.4% at baseline) with type 2 diabetes mellitus, who showed no evidence of retinopathy and had a mean known duration of diabetes of six years.²⁹ The researchers observed that 28% of participants developed mild to moderate retinopathy, but did not develop sight threatening or referable retinopathy in the form of severe preproliferative or proliferative retinopathy during the three year study period. However, they did identify macular oedema in three people, one of whom needed laser treatment.

Several studies, including the Liverpool Diabetic Eye Study,²⁶ similarly found that the incidence of diabetic retinopathy was

associated with the duration of diabetes and the use of insulin treatment.³³⁻³⁶ A younger age at diagnosis of diabetes has also been linked with increased incidence of retinopathy,³³ although this association was not found in the UK Prospective Diabetes Study.³⁷ In agreement with previous studies,^{26 37} we found no relation between the incidence of retinopathy and participants' sex, but we found a strong association between incidence and the use of insulin treatment, presumably indicating the stage of the disease.

Therefore, on the present evidence, annual screening is not necessary for people with type 2 diabetes with no lesions of diabetic retinopathy seen on digital images. Exceptions would include people with a duration of diabetes of 10 years or more and on insulin treatment, who should be retained on annual screening. If the screening service used a screening interval longer than 1 year, it would need to use safeguards to ensure that if patients changed risk groups within the year, a new appropriate interval would apply. Safeguards would include the education of patients and professionals to be aware of signs or symptoms suggestive of sight threatening retinopathy, and robust communication between healthcare professionals and the screening service. As electronic patient records become more widespread, these objectives could be more readily achievable.

Not all people classified as having referable diabetic retinopathy, for the purpose of screening, need urgent treatment at the first ophthalmological review. This is because most of these referrals are for isolated exudates (exudative maculopathy) without associated leakage (macular oedema) and early preproliferative retinopathy that need further investigations with fluorescein angiography or optical coherence tomography to determine high risk features. Laser treatment for such changes is not indicated, according to the Early Treatment of Diabetic Retinopathy Study,³ although focal laser treatment is considered for clinically important macular oedema. Early preproliferative retinopathy is also generally not treated in the first instance, since such cases are monitored for progression to high risk features and sometimes these retinal signs can resolve with improvement of glycaemic control.

The decision to treat is based on various factors, such as severity and status of the fellow eye, diabetes control, blood pressure, and lipid status. Clearly, if proliferative diabetic retinopathy is evident, early treatment with pan retinal photocoagulation can prevent the loss of vision.² A delay in diagnosing early exudative maculopathy or preproliferative retinopathy should not necessarily result in a poor outcome, since most diagnosed patients would enter a period of observation by the ophthalmologist after referral.

Future research

Our future research will explore the implications of varying the screening interval using risk stratification. To better predict the development of retinopathy, further research should investigate additional risk factors (for example, the individual and collective effects of glycaemic control (HbA_{1c}), blood pressure, albumin excretion, and lipid status, as well as possible treatments). These findings could improve risk stratification by better defining safe screening intervals on an individual basis. Another important area to investigate further includes the economic effect of the different screening intervals.

Conclusion and implications for policy makers

Other screening programmes have been able to revise their screening intervals based on evidence—that is, cervical,³⁸

breast,³⁹ and bowel⁴⁰ screening programmes in the UK. The original recommendation to undertake annual screening for diabetic retinopathy was based on a consensus view of experts and the over-riding wish to include such findings as part of the annual review for people with diabetes. Much debate has surrounded the appropriate screening interval for retinopathy screening, and although the American Diabetes Association recently recommended yearly screening, it suggested less frequent screening in people with at least one previous negative screen.⁴¹

Our study shows that the annual incidence of referable diabetic retinopathy is low in people with type 2 diabetes mellitus and without evidence of retinopathy at initial screening. These results lend further support to the suggestion of an extension to the screening interval beyond the 12 months currently adopted (although rarely achieved), with the possible exception of patients with a known duration of diabetes of longer than 10 years and on insulin treatment, who should continue to be screened annually. People who develop background retinopathy should also continue annual screening to avoid any delay in referral to ophthalmology services should sight threatening retinopathy develop, as adopted by the Icelandic screening service.²⁵

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Data sharing: No additional data available

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What is already known on this topic

- Screening for diabetic retinopathy is cost effective
- Diabetic retinopathy remains the leading cause of blindness in the working age population
- Previous studies have questioned the need for annual screening

What this study adds

- For people with type 2 diabetes mellitus with no evidence of diabetic retinopathy at initial screening, the interval of screening could be extended beyond the 12 months currently adopted, but rarely achieved. Possible exceptions are patients with a history of diabetes of 10 years or more and on insulin treatment, who should continue to be screened annually
- Future research should focus on a more comprehensive risk stratification as a basis for defining safe screening intervals

Tables

Table 1| Baseline characteristics of study participants

Characteristics	Participants without evidence of diabetic retinopathy at initial screening		P
	Did not attend a further screening event (n=6897)*	Attended at least one further screening event (n=49 763)	
Age (years)†	66.9 (13.5)	64.4 (11.3)	<0.001
Known duration of diabetes mellitus (years)†	4.6 (4.8)	4.2 (4.4)	<0.001
Age at diagnosis of diabetes mellitus (years)†	62.3 (13.2)	60.2 (11.3)	<0.001
Sex‡			
Male	3794 (55.0)	27 529 (55.3)	0.087
Female	3175 (46.0)	21 975 (44.2)	
Unknown	18 (0.3)	259 (0.5)	
Treatment for diabetes mellitus‡			
Diet	2684 (38.9)	17 236 (34.6)	<0.001
Oral hypoglycaemic agents	3787 (54.9)	29 049 (58.4)	
Insulin	394 (5.7)	2669 (5.4)	
Unknown	122 (1.8)	809 (1.6)	

*Group includes eligible participants only. †Mean (standard deviation). ‡Number (%).

Table 2| Yearly incidence of any and referable diabetic retinopathy in participants without retinopathy at baseline

Time from last negative screen	Any retinopathy		Referable retinopathy	
	Annual incidence	Cumulative incidence	Annual incidence	Cumulative incidence
1 year	124.94 (120.62 to 128.32)	124.94 (120.62 to 128.32)	2.02 (1.63 to 2.44)	2.02 (1.63 to 2.44)
2 years	91.68 (89.67 to 93.66)	216.81 (211.50 to 220.04)	2.82 (2.51 to 3.12)	4.85 (4.29 to 5.43)
3 years	76.96 (74.96 to 79.30)	293.80 (287.34 to 297.76)	3.24 (2.76 to 3.68)	8.09 (7.20 to 8.93)
4 years	66.59 (64.67 to 68.92)	360.27 (352.98 to 366.06)	3.54 (2.89 to 4.21)	11.64 (10.27 to 13.00)

Data are incidence (95% confidence interval) per 1000 people. Incidence of background retinopathy is the difference between the incidences of any and referable retinopathy.

Table 3| Yearly incidence of any and referable diabetic retinopathy in participants using insulin treatment and without retinopathy at baseline

Time from last negative screen	Any retinopathy		Referable retinopathy	
	Annual incidence	Cumulative incidence	Annual incidence	Cumulative incidence
1 year	192.43 (177.70 to 206.50)	192.43 (177.70 to 206.50)	2.56 (1.13 to 4.70)	2.56 (1.13 to 4.70)
2 years	128.03 (120.00 to 136.85)	320.64 (304.86 to 334.53)	5.00 (3.33 to 6.50)	7.67 (4.78 to 10.71)
3 years	100.19 (92.02 to 109.50)	421.62 (403.10 to 437.67)	6.84 (4.23 to 9.43)	14.48 (9.68 to 18.66)
4 years	81.69 (74.32 to 89.49)	502.95 (482.26 to 525.51)	8.41 (4.40 to 12.90)	22.81 (15.20 to 30.30)

Data are incidence (95% confidence interval) per 1000 people. Incidence of background retinopathy is the difference between the incidences of any and referable retinopathy.

Table 4| Baseline characteristics of participants according to outcome

	No retinopathy (n=36 841)*	Any retinopathy (n=12 922)	P	Referable retinopathy (n=348)	P
Age (years)†	64.2 (11.3)	64.9 (11.3)	0.002	62.9 (11.3)	0.005
Known duration of diabetes mellitus (years)†	3.9 (4.2)	5.1 (4.9)	<0.001	5.6 (5.4)	<0.001
Age at diagnosis of diabetes mellitus (years)†	60.3 (11.3)	59.8 (11.5)	<0.001	57.3 (11.8)	<0.001
Sex‡					
Male	20 346 (55.5)	7183 (55.9)	0.232	195 (56.2)	0.786
Female	16 316 (44.5)	5659 (44.1)		152 (43.8)	
Treatment for diabetes mellitus‡					
Diet	13 918 (38.5)	3318 (26.0)	<0.001	72 (20.7)	<0.001
Oral hypoglycaemic agents	20 723 (57.3)	8326 (64.4)		234 (67.2)	
Insulin	1555 (4.3)	1114 (8.6)		42 (12.1)	

*Reference group. †Mean (standard deviation). ‡Number (%).

Table 5| Parametric survival analysis with covariates in participants who developed diabetic retinopathy, according to grading category

Putative risk factor	Any retinopathy		Background retinopathy		Referable retinopathy	
	Crude hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)	Crude hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)	Crude hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)
Known duration of diabetes mellitus						
<5 years	1.00	1.00	1.00	1.00	1.00	1.00
5-9 years	1.39 (1.34 to 1.45)	1.29 (1.23 to 1.34)	1.39 (1.34 to 1.45)	1.29 (1.23 to 1.34)	1.54 (1.21 to 1.96)	1.35 (1.05 to 1.73)
≥10 years	1.92 (1.74 to 1.93)	1.68 (1.59 to 1.77)	1.82 (1.73 to 1.92)	1.67 (1.58 to 1.76)	1.99 (1.49 to 2.66)	1.61 (1.19 to 2.19)
Age at diagnosis						
30-49 years	1.00	1.00	1.00	1.00	1.00	1.00
50-59 years	0.93 (0.89 to 0.98)	0.97 (0.92 to 1.02)	0.94 (0.89 to 0.99)	0.97 (0.92 to 1.02)	0.71 (0.54 to 0.94)	0.75 (0.57 to 0.99)
60-69 years	0.90 (0.86 to 0.95)	0.99 (0.94 to 1.05)	0.91 (0.87 to 0.96)	1.00 (0.95 to 1.06)	0.50 (0.37 to 0.67)	0.57 (0.42 to 0.77)
≥70 years	0.98 (0.03 to 1.03)	1.20 (1.13 to 1.27)	0.98 (0.93 to 1.04)	1.20 (1.13 to 1.27)	0.64 (0.47 to 0.88)	0.83 (0.60 to 1.16)
Treatment for diabetes mellitus						
Diet	1.00	1.00	1.00	1.00	1.00	1.00
Oral hypoglycaemic agents	1.48 (1.43 to 1.55)	1.41 (1.36 to 1.47)	1.48 (1.43 to 1.55)	1.42 (1.36 to 1.48)	1.78 (1.36 to 2.32)	1.61 (1.22 to 2.12)
Insulin	2.35 (2.19 to 2.51)	2.03 (1.89 to 2.18)	2.34 (2.19 to 2.51)	2.03 (1.89 to 2.18)	3.39 (2.32 to 4.97)	2.60 (1.73 to 3.90)

All factors were significant at P<0.001.

CORRECTIONS

Incidence of diabetic retinopathy in people with type 2 diabetes mellitus attending the Diabetic Retinopathy Screening Service for Wales: retrospective analysis

In the online version of this paper (*BMJ* 2012;344:e874, doi:10.1136/bmj.e874) by Rebecca L Thomas and colleagues, the last sentence in the Results section should have been: "For participants with a duration of diabetes of 10 years or more, the use of insulin treatment increased cumulative incidence greatly

(without insulin treatment 2.24, 5.86, and 10.33 per 1000 people; with insulin treatment 9.61, 17.10, and 24.26 per 1000 people)."

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Appendix 2 Thomas RL et al. Ethnic differences in the prevalence of diabetic retinopathy in persons with diabetes when first presenting at a diabetes clinics in South Africa Diabetes Care 2013; 36: 336-341

Ethnic Differences in the Prevalence of Diabetic Retinopathy in Persons With Diabetes When First Presenting at a Diabetes Clinic in South Africa

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OBJECTIVE—To describe the prevalence and associated risk factors for diabetic retinopathy (DR) within a multiethnic population at presentation to a diabetes clinic in South Africa.

RESEARCH DESIGN AND METHODS—Retinal photography was conducted using a nonmydriatic digital camera without mydriasis and graded by one of three senior graders. Logistic regression analyses were used to assess the association between any DR, referable DR, and clinical risk factors.

RESULTS—A total of 1,537 persons with type 1 and 3,978 with type 2 diabetes were included. Prevalence of any DR in type 1 diabetes was 35.2% (background DR 26% and referable DR 9.2%) and in type 2 diabetes was 20.5% (14.1 and 6.4%, respectively). In type 1 diabetes, there was an increased risk of any DR in Asian Indians, whereas the risk of referable DR was increased for indigenous Africans compared with Caucasians. In type 2 diabetes, the risk was increased for all non-Caucasians compared with Caucasians. Longer duration of diabetes and elevated HbA_{1c} were independently associated with any and referable DR in both type 1 and type 2 diabetes, with the addition of hypertension and smoking in type 1 diabetes when adjusted for age at diagnosis of diabetes, sex, and ethnicity.

CONCLUSIONS—The prevalence of DR in this population from South Africa was similar to that reported globally; however, ethnic differences were observed. Increasing duration of diabetes and poor glycemic control were the strongest risk factors associated with any and referable DR in both type 1 and type 2 diabetes.

Diabetes Care 36:336–341, 2013

South Africa has an estimated population of ~50 million inhabitants, the majority being indigenous Africans (79.5%) with a minority comprising Caucasian (9%), mixed race (9%), and Asian Indians (2.5%) (1). The health care provider system in South Africa consists of a large and under-resourced public sector and a smaller, fast-growing private health care sector. Health care varies from the most basic primary health care, which is provided free by the state to ~80% of the population, to highly

specialized services available in the private sector (2). It has been estimated that the prevalence of diabetes in South Africa is 5–10% of the population (3), with only ~11% of those with diabetes having their eyes routinely examined for diabetic retinopathy (DR) (4).

There is some evidence to suggest that the risk of DR and blindness in South Africa can vary with ethnicity (5–8). This in part may be due to increased prevalence and impact of additional putative risk factors for DR or as yet unidentified

risk factors for DR. Recently, the global prevalence of DR has been reported to be 55.8% in African Americans, 46.7% in Caucasians, and 20.9% in Asians (9). To date, the reported prevalence of DR in South Africa's public sector has ranged between 14 and 55% in indigenous Africans, 41% in Caucasians, and 22 and 37% in Asian Indians with diabetes (10–12). The aim of this study was to describe the prevalence of DR within a defined population with diabetes attending, for the first time, a private diabetes clinic, the Centre for Diabetes and Endocrinology (CDE) in Johannesburg, South Africa, and to identify the associated risk factors as well as explore any ethnic variations in the prevalence of DR. Prevalence figures are essential in order to estimate current and future burden of disease and benefits that may result from the implementation of a DR-screening service.

RESEARCH DESIGN AND METHODS

Setting

The CDE is a private multispecialist center based in Johannesburg, South Africa, established in 1994. It serves as the principal center in a network of 262 smaller urban and rural centers providing diabetes care services in underdeveloped communities in South Africa. Details of the diabetes management program of the CDE have been described in detail previously (13).

Methods

All persons with diabetes attending the CDE undergo routine digital retinal photography performed at the time of their first visit and annually thereafter. Digital retinal photography was conducted in a darkened room using a nonmydriatic digital camera (Canon CR6–45NM; Canon) capturing one macular centered image per eye without the use of mydriasis by one of two trained technicians, one of whom is a diabetes nurse educator. All retinal images from the patient's first

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screening event obtained from 2001–2010 were independently reviewed and graded by one of three senior retinal graders according to a modified U.K. standard DR-grading protocol used by the DR Screening Service for Wales (14). Levels of DR were classified as no DR (NDR) if no lesions were detected, any DR when at least one microaneurysm and/or a blot hemorrhage were detected, and referable DR (RDR), which included preproliferative and proliferative lesions of DR as well as exudative maculopathy. RDR is the level at which further assessment by an ophthalmologist is deemed necessary.

Subjects included in this analysis were classified as having type 1 or type 2 diabetes on clinical assessment according to the American Diabetes Association classification of diabetes (9). Those individuals who did not clinically clearly fit into this classification were excluded from the analysis.

At the time of initial presentation, when the first retinal photographs were taken, blood was obtained for baseline laboratory investigations including HbA_{1c}, lipid analyses, and serum creatinine, and urine was collected for the assessment of the microalbumin/creatinine ratio. This initial HbA_{1c} was regarded as the baseline value and used in the analysis. The HbA_{1c} was initially analyzed as Diabetes Control and Complications Trial (DCCT) percent values and then converted to International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) mmol/mol units using the formula: [DCCT percent – 2.15] × 10.929. Both DCCT and IFCC units are dually reported throughout. Subjects were considered to have hypertension if their blood pressure was found to be >140/90 mmHg taken in the right arm seated after 5-min rest and/or if they were already on antihypertensive therapy. Other variables such as BMI were not available for analysis in this study.

Statistical analysis was conducted using SPSS version 16 (SPSS) and the population characteristics described using means and SDs for normally distributed and medians and interquartile ranges (IQ) for nonnormally distributed continuous variables and percentages for categorical variables. Significance testing used: *t* tests and Mann-Whitney *U* tests for continuous variables and χ^2 for categorical variables. Stepwise logistic regression analysis was used to assess the association of clinical risk factors and the presence of any DR and RDR for persons with type 1 and type 2 diabetes

separately. Odds ratios (OR) and 95% CI were calculated for each. The continuous variables (HbA_{1c} and duration of diabetes) were stratified to avoid assumptions of linearity (i.e., for type 1 diabetes): HbA_{1c} <7.0 (<53), 7.0–7.9% (53–63), 8.0–8.9% (64–74), and ≥9.0% (≥75 mmol/mol) and duration of diabetes <7, 7–15, and >15 years; and for type 2 diabetes: HbA_{1c} <6.6 (<49), 6.6–7.4 (49–57), 7.5–8.9 (58–74) and ≥9.0% (≥75 mmol/mol) and known duration of diabetes <3, 3–8, and >8 years. Different stratifications were used in those with type 1 and type 2 diabetes for HbA_{1c} and duration of diabetes to ensure an equal distribution among the strata for both diabetes types. Associations were considered significant if the *P* value was <0.05.

RESULTS—A total of 5,565 subjects were seen at the CDE in Johannesburg during 2001 and 2010. The majority of people had type 2 diabetes (71.5%), with 27.6% having type 1 diabetes. The remaining 0.9% had other forms of diabetes and were excluded from the analysis. The

baseline characteristics of the population studied are listed in Table 1.

Type 1 diabetes

In persons with type 1 diabetes, those of Caucasian origin had a longer duration of diabetes (*P* < 0.001), were younger at diagnosis (*P* < 0.001), and had a lower HbA_{1c} at presentation (*P* < 0.001) compared with the non-Caucasian population. Among the non-Caucasians, indigenous Africans had a shorter duration of diabetes compared with those of mixed race (*P* = 0.026) and were older at diagnosis than either the Asian Indians (*P* = 0.004) or those of mixed race (*P* = 0.004) (Table 2).

There was no evidence of DR in 60.3% (95% CI 57.8–62.7; *n* = 927), background DR was detected in 26% (95% CI 23.8–28.2; *n* = 399), and RDR in 9.2% (95% CI 7.9–10.8; *n* = 142). The RDR category consisted of 1.2% (95% CI 0.7–1.8; *n* = 18) with preproliferative DR, 4.9% (95% CI 3.9–6.1; *n* = 75) had exudative maculopathy, 1.3% (95% CI 0.8–2.0; *n* = 20) preproliferative DR with exudative maculopathy, 1.0% (95% CI 0.6–1.6; *n* = 15)

Table 1—Baseline* characteristics for persons with diabetes

Characteristics	Type 1 diabetes (<i>n</i> = 1,537)	Type 2 diabetes (<i>n</i> = 3,978)	All subjects (<i>n</i> = 5,515)
Age (years) [mean (SD)]	35.4 (15.4)	56.8 (11.8)	50.8 (16.1)
Sex [<i>n</i> (%)]			
Male	846 (55.0)	2,650 (66.6)	3,496 (63.4)
Female	690 (44.9)	1,326 (33.3)	2,016 (36.6)
Unknown	1 (0.1)	2 (0.1)	3 (0.1)
Ethnicity [<i>n</i> (%)]			
Caucasian	1,247 (81.1)	2,662 (66.9)	3,909 (70.9)
Indigenous African	117 (7.6)	580 (14.6)	697 (12.6)
Asian	118 (7.7)	562 (14.1)	680 (12.3)
Mixed race	49 (3.2)	159 (4.0)	208 (3.8)
Unknown	6 (0.4)	15 (0.4)	21 (0.4)
Duration of DM (years) [median (IQ)]	11.0 (5.0–19.0)	5.0 (1.0–10.0)	6.0 (2.0–12.0)
Age at diagnosis DM (years) [mean (SD)]	22.3 (13.8)	50.1 (11.9)	42.3 (17.6)
HbA _{1c} (%) [median (IQ)]	8.4 (7.3–9.8)	7.5 (6.6–8.9)	7.7 (6.8–9.2)
HbA _{1c} (mmol/mol) [median (IQ)]	68 (56–84)	58 (49–74)	61 (51–77)
Total cholesterol (mmol/L) [mean (SD)]	5.1 (1.1)	5.0 (1.2)	5.0 (1.2)
Albumin/creatinine ratio [median (IQ)]	0.9 (0.4–2.1)	1.1 (0.5–3.6)	1.0 (0.5–3.0)
Other therapies [<i>n</i> (%)]			
ACE	253 (16.5)	1,620 (40.7)	1,873 (34.0)
Aspirin	44 (2.9)	743 (18.7)	787 (14.3)
Hypertensive [<i>n</i> (%)]	287 (18.7)	2,141 (53.8)	2,428 (44.0)
Smoker [<i>n</i> (%)]	302 (19.6)	607 (15.3)	909 (16.5)
Retinopathy [<i>n</i> (%)]			
Unassessable	69 (4.5)	194 (4.9)	263 (4.8)
NDR	927 (63.1)	2,968 (78.4)	3,895 (74.2)
Any DR	541 (36.9)	816 (21.4)	1,357 (25.8)
RDR	142 (9.7)	255 (6.6)	397 (7.5)

*At presentation to CDE.

Table 2—Baseline* characteristics for the different ethnic groups for persons with type 1 and type 2 diabetes

	Caucasian	Non-Caucasians	P value†	Indigenous African	Asian	Mixed race	P value‡
Type 1 diabetes							
n	1,247	284		117	118	49	
Age (years) [mean (SD)]	35.7 (15.6)	34.0 (14.5)	0.075	36.3 (16.1)	32.2 (12.1)	32.6 (15.2)	0.069
Sex [n (%)]			0.570				0.253
Male	690 (55.3)	152 (53.5)		66 (56.4)	65 (55.1)	21 (42.9)	
Female	556 (44.6)	132 (46.5)		51 (43.6)	53 (44.9)	28 (57.1)	
Unknown	1 (0.1)	0		0	0	0	
Duration of DM (years) [median (IQ)]	12.0 (6.0–20.0)	7.0 (3.0–13.0)	<0.001	5.0 (3.0–11.5)	8.0 (3.0–15.0)	8.0 (5.0–14.5)	0.070
Age at diagnosis (years) [mean (SD)]	21.6 (13.6)	25.0 (14.2)	<0.001	28.5 (15.5)	22.7 (11.8)	22.7 (14.6)	0.003
HbA _{1c} (%) [median (IQ)]	8.2 (7.3–9.6)	9.0 (7.7–11.2)	<0.001	9.5 (7.8–11.3)	8.7 (7.6 to 10.9)	9.0 (7.3–11.4)	0.272
HbA _{1c} (mmol/mol) [median (IQ)]	66 (56–81)	75 (61–99)	<0.001	80 (62–100)	72 (60–96)	75 (56–101)	0.272
Type 2 diabetes							
n	2,662	1,296		580	562	159	
Age (years) [mean (SD)]	59.7 (11.1)	50.9 (10.9)	<0.001	51.7 (10.0)	50.5 (11.8)	49.5 (10.7)	0.037
Sex [n (%)]			0.008				0.013
Male	1,810 (68.0)	829 (63.7)		382 (65.9)	362 (64.4)	85 (53.5)	
Female	851 (32.0)	471 (36.2)		197 (34.0)	200 (35.6)	74 (46.5)	
Unknown	1 (0.0)	1 (0.1)		1 (0.2)	0	0	
Duration of DM (years) [median (IQ)]	5.0 (1.0–10.0)	5.0 (2.0–10.0)	0.073	5.0 (2.0–10.0)	5.0 (1.0–10.0)	4.0 (1.0–10.0)	0.173
Age at diagnosis (years) [mean (SD)]	53.0 (11.4)	44.0 (10.7)	<0.001	44.6 (9.8)	43.5 (11.5)	43.7 (10.3)	0.199
HbA _{1c} (%) [median (IQ)]	7.3 (6.5–8.4)	8.1 (6.9–10.0)	<0.001	8.3 (7.0–10.5)	7.9 (6.9–9.4)	8.1 (7.0–10.0)	0.003
HbA _{1c} (mmol/mol) [median (IQ)]	56 (48–68)	65 (52–86)	<0.001	67 (53–91)	63(52–79)	65 (53–86)	0.003

*At presentation to CDE. †P value differences between Caucasians and non-Caucasians. ‡P value for differences across the non-Caucasian groups. DM, diabetes.

proliferative DR, and 0.9% (95% CI 0.5–1.5; $n = 14$) proliferative DR with exudative maculopathy. There were 4.5% (95% CI 3.6–5.6; $n = 69$) unassessable images mainly due to the presence of lens opacification.

Those who presented with any or RDR compared with those with NDR were older [mean (SD)]: 38.0 (13.6) and 38.6 (12.2) years versus 32.9 (15.6) years, respectively ($P < 0.001$); and were younger at diagnosis of diabetes: 19.6 (11.8) and 19.0 (11.4) years versus 23.5 (14.4) years, respectively ($P < 0.001$), with a longer duration of diabetes [median (IQ)]: 17.0 (12.0–23.0) and 18.0 (14.0–25.0) years versus 6.0 (3.0–12.0) years, respectively ($P < 0.001$). Those presenting with any or referable levels of DR compared with those without DR also had a higher HbA_{1c} level: 8.5 (7.6–9.9)% (69 [60–85] mmol/mol), 8.7 (7.8–10.2)% (72 [62–88] mmol/mol) versus 8.3 (7.1–9.7)% (67 [54–83] mmol/mol), respectively (any DR vs. NDR, $P = 0.033$; RDR vs. NDR, $P = 0.013$) and had a higher prevalence of hypertension (25.1 and 35.9%

RDR versus 12.1%, respectively; $P < 0.001$). There were also more cigarette smokers with any DR or RDR compared with those without DR (22.9 and 22.5% versus 17.6%, respectively; $P = 0.013$). (Only one P value is shown in the text, as the P value is similar for the comparison between any DR versus NDR and RDR versus NDR.)

In logistic regression analyses, the presence of any DR and RDR was significantly associated with ethnicity (Table 3). Asian Indians were at an increased risk of any DR (OR 1.78) when compared with Caucasians and adjusted for age at diagnosis, sex, duration of diabetes, HbA_{1c}, hypertension, and smoking status. In comparison, indigenous Africans had an increased risk of RDR (OR 3.36). There was no significant difference for any DR or RDR comparing those of mixed race with Caucasians. Other risk factors independently associated with any DR (Table 3) were a longer duration of diabetes (OR 10.28, 7–15 years; 37.31, >15 years; reference group <7 years), an increased HbA_{1c} (OR 1.32, <7.0% [<53 mmol/

mol]; 2.15, 8.0–8.9% [64–74 mmol/mol]; and 3.20, $\geq 9.0\%$ [≥ 75 mmol/mol]; reference group >7.0% [>53 mmol/mol]), the presence of hypertension (OR 1.44), and the habit of smoking (OR 1.78). The presence of RDR was also significantly associated with duration of diabetes, HbA_{1c}, hypertension, and smoking. There was a weak but significant association between albumin/creatinine ratio and any DR and RDR in univariate analysis; however, these data were missing for many of the persons with diabetes and were therefore removed from the stepwise multivariate analyses.

Type 2 diabetes

Caucasian subjects with type 2 diabetes were older at baseline and at the time of diagnosis ($P < 0.001$) and had a lower HbA_{1c} ($P < 0.001$) than non-Caucasians (Table 2). The known duration of diabetes was similar across all ethnicities. There were differences in sex distribution, with more males of Caucasian ethnicity compared with non-Caucasians ($P = 0.008$) and more females of mixed race compared

Table 3—Multivariate logistic regression analysis of independent risk factors for any and RDR in persons with type 1 and type 2 diabetes (adjusted for age at diagnosis of diabetes and sex)

	Any DR (n = 541)		RDR (n = 142)	
	Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)
Type 1 diabetes				
Ethnicity (n)				
Caucasian (1,247)	1.00	1.00	1.00	1.00
Indigenous African (117)	0.71 (0.46–1.09)	1.72 (1.00–2.97)	0.95 (0.49–1.84)	3.40 (1.40–8.26)
Asian (118)	1.10 (0.74–1.63)	2.02 (1.23–3.29)	1.05 (0.54–2.04)	2.07 (0.90–4.75)
Mixed race (49)	1.01 (0.56–1.84)	1.29 (0.62–2.69)	1.10 (0.42–2.88)	1.06 (0.36–3.18)
Duration of DM (years) (n)				
<7 (505)	1.00	1.00	1.00	1.00
7–15 (515)	8.89 (6.01–13.15)	10.28 (6.75–15.65)	16.19 (5.75–45.60)	20.08 (6.81–59.18)
>15 (517)	26.20 (17.62–38.95)	37.31 (23.57–59.07)	68.74 (24.89–189.88)	116.06 (38.00–354.43)
HbA _{1c} (%) (n)				
<7.0 ^a (310)	1.00	1.00	1.00	1.00
7.0–7.9 ^b (342)	1.78 (1.26–2.52)	1.32 (0.88–1.97)	1.15 (0.62–2.12)	0.95 (0.47–1.89)
8.0–8.9 ^c (322)	2.15 (1.52–3.04)	2.15 (1.43–3.25)	1.79 (1.01–3.19)	1.99 (1.02–3.90)
≥9.0 ^d (563)	2.05 (1.50–2.81)	3.20 (2.17–4.71)	2.06 (1.23–3.44)	4.07 (2.18–7.62)
Albumin/creatinine ratio (n = 647)	1.06 (1.03–1.09)		1.08 (1.04–1.01)	
Hypertension (n = 302)	2.44 (1.85–3.22)	1.44 (1.02–2.03)	4.08 (2.75–6.06)	2.41 (1.47–3.96)
Smoking (n = 287)	1.39 (1.07–1.81)	1.78 (1.28–2.47)	1.36 (0.89–2.09)	2.15 (1.27–3.65)
Any DR (n = 816)				
RDR (n = 255)				
Type 2 diabetes				
Ethnicity (n)				
Caucasian (2,662)	1.00	1.00	1.00	1.00
Indigenous African (580)	2.00 (1.62–2.48)	1.79 (1.40–2.30)	3.69 (2.71–5.02)	3.08 (2.14–4.43)
Asian (562)	1.83 (1.48–2.26)	1.59 (1.24–2.04)	1.93 (1.34–2.80)	1.57 (1.04–2.39)
Mixed race (159)	2.66 (1.88–3.76)	2.69 (1.80–4.02)	3.52 (2.08–5.95)	3.27 (1.78–6.04)
Known duration of DM (years) (n)				
<3 (1,391)	1.00	1.00	1.00	1.00
3–8 (1,360)	2.61 (2.02–3.36)	2.33 (1.80–3.03)	2.36 (1.41–3.95)	2.05 (1.21–3.46)
>8 (1,224)	11.24 (8.8–14.28)	9.59 (7.46–12.32)	18.03 (11.47–28.34)	14.98 (9.37–23.95)
HbA _{1c} (%) (n)				
<6.5 ^e (966)	1.00	1.00	1.00	1.00
6.5–7.4 ^f (1,097)	1.61 (1.25–2.09)	1.32 (1.00–1.75)	1.75 (1.05–2.94)	1.46 (0.85–2.51)
7.5–8.9 ^g (1,008)	2.77 (2.16–3.55)	1.84 (1.40–2.41)	3.84 (2.38–6.18)	2.43 (1.47–4.03)
≥9.0 ^h (97)	3.86 (3.01–4.95)	2.25 (1.71–2.96)	6.93 (4.37–10.99)	3.68 (2.25–6.03)
Albumin/creatinine ratio (n = 1,483)	1.03 (1.02–1.05)		1.04 (1.02–1.05)	
Hypertension (n = 607)	1.35 (1.15–1.57)		1.54 (1.18–2.00)	
Smoking (n = 2,141)	0.98 (0.79–1.21)		0.75 (0.51–1.10)	

^a<53 mmol/mol. ^b53–66 mmol/mol. ^c64–74 mmol/mol. ^d≥75 mmol/mol. ^e<48 mmol/mol. ^f48–57 mmol/mol. ^g58–74 mmol/mol. ^h75 mmol/mol. DM, diabetes.

with indigenous Africans and Asian Indians ($P < 0.013$). There was also a difference in age and HbA_{1c} levels between those of non-Caucasian ethnicity with those indigenous Africans who were older ($P = 0.037$) and with higher HbA_{1c} levels ($P = 0.003$) compared with Asian Indians and mixed races (Table 2).

In the entire cohort of subjects with type 2 diabetes, the prevalence of any DR was 20.5% (95% CI 19.3–21.8), with NDR detected in 74.6% (95% CI 73.2–75.9; $n = 2,968$). The majority of DR seen was background DR: 14.1% (95% CI 13.1–15.2; $n = 561$), with 6.4% (95% CI 5.7–7.2;

$n = 255$) having RDR. The category of RDR consisted of 0.7% (95% CI 0.5–1.0; $n = 28$) preproliferative DR, 3.5% (95% CI 3.0–4.2, $n = 141$) exudative maculopathy, 1.4% (95% CI 1.0–1.8; $n = 54$) preproliferative DR with exudative maculopathy, 0.2% (95% CI 0.1–0.4; $n = 8$) proliferative DR, and 0.6% (95% CI 0.4–0.9; $n = 24$) proliferative DR with exudative maculopathy. There was a similar proportion with unassessable images (4.8%; 95% CI 4.3–5.6) with type 2 diabetes as seen in the subjects with type 1 diabetes.

Those presenting with any or RDR compared with those without DR were

younger at diagnosis of diabetes (mean [SD]) (45.8 [11.4] years for any DR or 43.9 [10.2] years RDR vs. 51.1 [11.7] years NDR; $P < 0.001$), had a longer known duration of diabetes (median [IQ]) (10.0 [6.0–16.0] years for any DR or 12.0 [8.0–17.0] years RDR vs. 3.0 [1.0–7.0] years NDR; $P < 0.001$), and had a higher HbA_{1c} level (8.2 [7.1–9.7]%; 66 [54–83] mmol/mol for any DR; or 8.7 [7.6–8.7]%; 72 [60–72] mmol/mol RDR vs. 7.3 [6.5–8.6]%; 56 [48–70] NDR; $P < 0.001$). There was also a higher proportion of persons with hypertension (59.2% any DR or 62.4% RDR vs. 51.9% NDR;

$P < 0.001$). There was a ($P < 0.001$) lower proportion of Caucasians than all other ethnic groups in those with any or RDR (16.8 and 4.4% Caucasians, 27.2 and 13.1% indigenous Africans, 27.0 and 7.5% Asian Indians, and 34.6 and 11.9% mixed race, respectively) compared with those without DR (78.9% Caucasian, 63.8% indigenous Africans, 69.4% Asian Indians, and 61.0% mixed race; Fig. 1). (Only one P value is shown in the text, as the P value is similar for the comparison between any DR versus NDR and RDR versus NDR.)

When compared with the Caucasian population, non-Caucasians had an increased risk of any DR (indigenous Africans 1.90, Asian 1.74, and mixed race 2.95) when adjusted for age at diagnosis of diabetes, sex, known duration of diabetes, and HbA_{1c} (Table 3). Other risk factors independently associated with any DR included a longer known duration of diabetes (OR 2.33, 3–8 years; 9.59, >8 years;

reference group <3 years) and an increased HbA_{1c} (OR 1.32 6.6–7.4% [49–57 mmol/mol]; 1.84, 7.5–8.9% [58–74 mmol/mol]; and 2.25, $\geq 9.0\%$ [≥ 75 mmol/mol]; reference group <6.6% [49 mmol/mol]). Non-Caucasian ethnicity increased known duration of diabetes and increased HbA_{1c} were also associated with RDR. Smoking was not associated with an increased risk of any DR or RDR. Although hypertension was associated with any DR and RDR in univariate analysis, it was not included in the results of stepwise multivariate analyses. Although there was a weak significant association between albumin/creatinine ratio and any DR and RDR in univariate analysis, these data were missing for the majority of patients and therefore removed from the stepwise analysis.

CONCLUSIONS—In a large cohort of persons with type 1 and type 2 diabetes undergoing retinal photography when

first presenting at the CDE, the overall prevalence of DR and RDR at the time of the first visit was 24.6 and 7.2%, respectively. The prevalence of any DR was lower than in the recent survey of the global prevalence of any DR of 34.6% (9). This is the first study to be conducted in the privately funded sector in South Africa, which may account for this difference.

Ethnic differences in the prevalence and associations with the presence of any DR (5,7,8) and also severe/referable stages of DR (6,7) have previously been reported to be higher in non-Caucasian persons when compared with Caucasians or Europeans. Only two previous studies, in relative numbers of persons with diabetes, have examined differences between ethnic groups in South Africa (4,10). One study did not report any significant associations between ethnicity and DR (4), and the other found that those of an African and Indian origin had a significantly higher prevalence of severe DR than Europeans (10). In contrast, we observed clear differences in the risk of DR between the ethnic groups studied. Although the risk of any DR was increased in Asian Indians, RDR was increased for indigenous Africans with type 1 diabetes when compared with Caucasians, and the risk of both any DR and RDR was increased for all non-Caucasian populations compared with Caucasians with type 2 diabetes. These differences remained after correction for other risk factors, which include the fact that those of African and mixed-race origin had higher HbA_{1c} levels at baseline and type 2 diabetes starting at a younger age than in the non-Caucasian population. Kalk et al. (10) also reported a higher prevalence of microalbuminuria in patients of indigenous African descent when compared with a Caucasian population. This suggests that ethnic differences exist in the propensity to develop microvascular complications such as DR.

Our study demonstrated that the presence of any DR and RDR were strongly associated with increasing duration of diabetes and a higher HbA_{1c} level in persons with both type 1 and type 2 diabetes, thus confirming earlier epidemiological studies (15,16). Previous epidemiological studies and clinical trials also indicate that hypertension is an important modifiable risk factor for DR (17–19). In this study however, hypertension was shown to be a significant risk factor only in persons with type 1 diabetes. A reason for the lack of an association for persons with type 2 diabetes may be due to the more aggressive

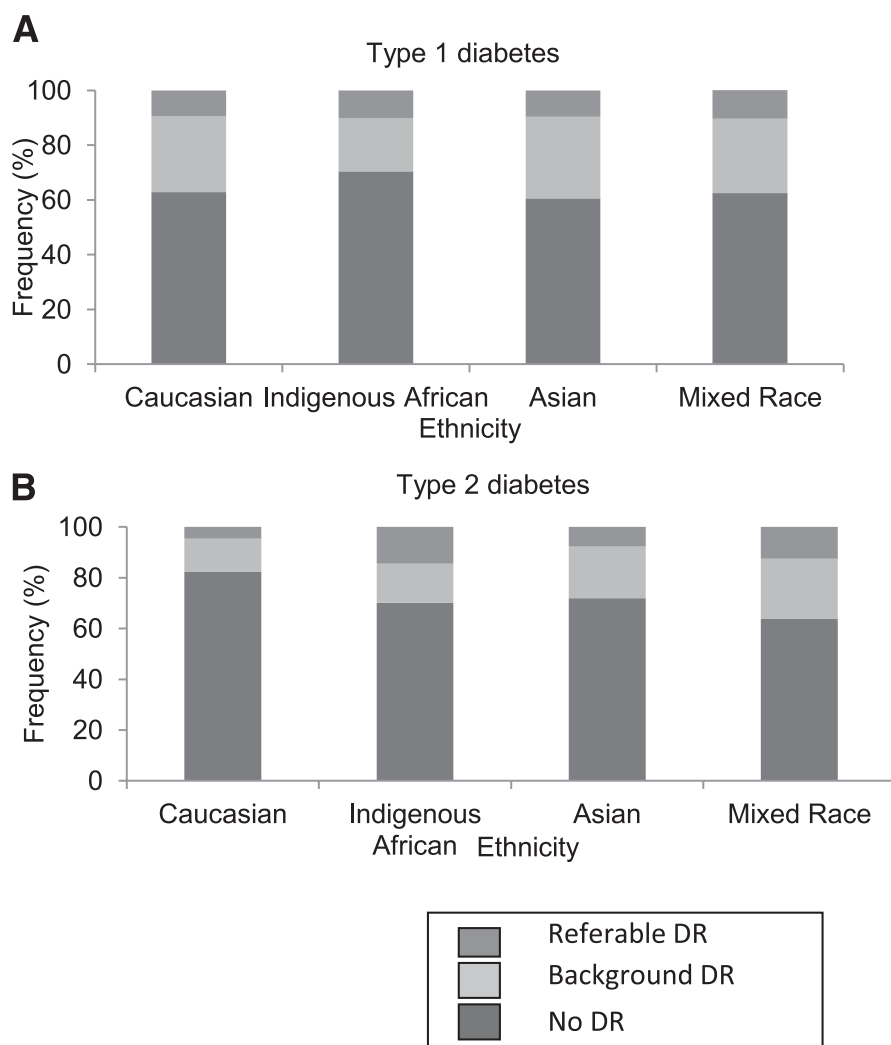


Figure 1—Frequency of DR by ethnic groups in persons with type 1 (A) and type 2 (B) diabetes.

treatment of hypertension and lower blood pressure targets in this patient group. The importance of smoking as a risk factor for DR is inconclusive, with some studies showing either an association (20–23) or even suggesting that smoking may be protective against the development of DR (24). In our study, smoking had a clear association with the development of referable retinopathy in patients with type 1 diabetes, but not those with type 2 diabetes.

Compared with previous population-based studies in Africa and South Africa, the strength of this study was the larger sample size and that all the data (i.e., retinal images and the putative risk factors) were derived from a single center (CDE). However, as most of the population in South Africa with diabetes uses the public health system, the population studied in this paper may not therefore be representative of this majority. Although the use of standardized digital retinal photography and grading protocol are strengths within this study, the lack of dilation may have led to a higher proportion of ungradeable images, and the availability of only one 45° field per eye may have resulted in underreporting of DR.

Long-term follow-up of the majority of the participants in this study, involving intensive diabetes and risk factor management, is underway at the CDE. This will allow assessment of the incidence of both newly developing DR and the progression of DR in this cohort of subjects with both type 1 and type 2 diabetes and will be the subject of a future report.

In this large population sample of individuals with diabetes entering a diabetes management program, there was a low prevalence of DR. Ethnicity was independently associated with the presence of DR and RDR in both type 1 and type 2 diabetes. Increasing duration of diabetes and poor glycemic control were the strongest risk factors associated with the presence of any and RDR in persons with both type 1 and type 2 diabetes. In type 1 diabetes, hypertension and smoking were additional risk factors for the presence of any and RDR.

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R.L.T., L.D., S.D.L., S.R.C., V.J.M., B.K., and D.R.O. contributed to the writing of this article and approved the final version of the manuscript. R.L.T. processed and analyzed data. L.D. was the lead for this study with the support of B.K. and D.R.O. L.D., S.D.L., B.K., and D.R.O. contributed to the concept, study

design, and interpretation of data. S.R.C. contributed to the processing of data. V.J.M. collated all data. D.R.O. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Prevalence of diabetic retinopathy within a national diabetic retinopathy screening service

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ABSTRACT

Aims Determine the prevalence and severity of diabetic retinopathy (DR) and risk factors in a large community based screening programme, in order to accurately estimate the future burden of this specific and debilitating complication of diabetes.

Methods A cross-sectional analysis of 91 393 persons with diabetes, 5003 type 1 diabetes and 86 390 type 2 diabetes, at their first screening by the community based National Diabetic Retinopathy Screening Service for Wales from 2005 to 2009. Image capture used 2×45° digital images per eye following mydriasis, classified by qualified retinal graders with final grading based on the worst eye.

Results The prevalence of any DR and sight-threatening DR in those with type 1 diabetes was 56.0% and 11.2%, respectively, and in type 2 diabetes was 30.3% and 2.9%, respectively. The presence of DR, non-sight-threatening and sight-threatening, was strongly associated with increasing duration of diabetes for either type 1 or type 2 diabetes and also associated with insulin therapy in those with type 2 diabetes.

Conclusions Prevalence of DR within the largest reported community-based, quality assured, DR screening programme, was higher in persons with type 1 diabetes; however, the major burden is represented by type 2 diabetes which is 94% of the screened population.

INTRODUCTION

Diabetic retinopathy (DR) continues to be an important microvascular complication in type 1 and type 2 diabetes. Previous evidence suggests that DR is evident in approximately 50% of persons with type 1 diabetes for 28 years and advanced DR after 39 years.¹ In contrast about 12–19%,^{2–3} of persons with type 2 diabetes have some DR already at the time of diagnosis,⁴ with 4% developing proliferative DR after 20 years or more of diabetes.² In the UK and USA, DR unfortunately remains among the leading causes of blindness and low vision, along with age related macular degeneration and glaucoma.^{5–8}

The St Vincent Declaration (1989) recommended that new onset blindness arising from DR should be reduced by a third within 5 years.⁹ However, it is only in the last decade that significant progress has been made in implementing screening programmes to detect and monitor DR. To date many different DR screening models have been introduced worldwide.^{10–19} In the UK the National Screening Committee for England and Wales (1999) produced guidelines for DR screening

programmes to ensure standardisation and quality assurance. The recommended screening procedure includes assessment of visual acuity and obtaining digital fundal photographs following mydriasis,²⁰ in persons aged 12 years and older.²¹ The recommendation of screening beginning from the age of 12 years reflects the low incidence of DR, and especially proliferative DR, in younger children.²² In Scotland a three tiered screening approach has been implemented which involves obtaining only one macular centred digital fundal photograph per eye without mydriasis (tier 1) and if unsuccessful then mydriasis is used (tier 2) and finally biomicroscopy with a slit lamp if photography remains unsuccessful (tier 3).²³

Wales currently has a population of 3.06 million which is predominantly Caucasian, with the majority situated in the industrial south (~60%) with the remainder of the country generally regarded as rural.²⁴ The prevalence of diabetes in Wales is currently estimated at approximately 5%, with 160 000 people affected.²⁵ Following a pilot regional programme,²⁶ a national DR screening programme, the Diabetic Retinopathy Screening Service for Wales (DRSSW) was commissioned in 2002. The aim of the service was initially to identify all undiagnosed sight-threatening DR and facilitate timely onwards referral to hospital eye services (HES). The secondary aim was to identify the presence of any DR so that improvements in glycaemic control, hypertension and dyslipidaemia could be implemented where necessary.²⁰

The prevalence of DR has previously been described for several populations,^{8–27} using different methods for the detection and classification of DR which accounts in part for the broad variations observed. A recent systematic review,²⁷ conducted an individual participant analysis to estimate the global prevalence of DR and also to determine the major risk factors by pooling a total 35 studies (22 896 people) conducted between 1980 and 2008 in the USA, Australia, Europe and Asia. The studies obtained retinal photographs using a mixture of 35 mm film and digital images, through dilated and undilated pupils capturing between one and nine fields per eye with a minority photographing one eye only. There were also several different grading protocols used to ascertain the prevalence and severity of DR.

The objective of our study was to accurately determine the prevalence of DR at entry into a national screening programme using standardised protocols and quality-assured methodology for

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photography and grading and also to explore the relationship between certain putative risk factors with the presence of any lesions of DR and also the presence of sight-threatening DR in persons with type 1 and type 2 diabetes.

MATERIALS AND METHODS

DRSSW is a community-based mobile screening service. Habitual Visual acuity (VA) is recorded (with or without glasses or with pinhole) using a 3 m illuminated Snellen chart and two 45° fields (one macula centred and one nasal) digital fundal photographs are captured following mydriasis (1% tropicamide) followed by grading by accredited retinal graders. Images are stored on laptop computers and then downloaded daily onto a central server, either directly or via a secure internet connection. DRSSW employs 30 photographic teams consisting of a health-care professional and an accredited photographer who conduct the screening at 220 locations throughout Wales. The Canon DGi digital camera is used to acquire the digital images which are centrally graded using a standardised grading protocol (table 1). All the key elements are subject to quality control procedures. At the time of screening all persons are asked to sign a two part consent form. The first part is to give consent for mydriasis to be instilled and for retinal photographs to be taken. The second part is for consent for their anonymised data and images to be used for teaching and research purposes. Only the data for those individuals who provided both consents were included in this study.

Persons with diabetes aged 12 years or above who are registered with a general practitioner (GP) in Wales and not already under the care of HES for DR related reasons, are required to be referred to DRSSW accompanied by demographic and diagnostic information. These referrals from GP's form the single collated list of persons for screening. On a monthly basis the lists are compiled and sent to each GP practice for validation. Of those known to have diabetes in Wales 8.4% were ineligible for screening as 6.5% were already under the care of HES for DR related reasons, 1.6% were excluded due to medical reasons and 0.4% were under the age of 12 years (19.3% of those who were eligible for screening did not attend appointments). All persons invited for screening are sent an appointment letter with a date, time and venue for screening. All letters have a reminder that all appointments and venues can be changed to a

time and place more suitable for the individual. DRSSW currently (2013) has an uptake rate of 80% for screening. Those who do not attend screening appointments are sent additional appointments within 3 months and their GPs are informed of their non-attendance and are asked to remind their patients of the importance of attending screening.

DRSSW uses a grading protocol which evolved from the European handbook for screening⁹ and all subsequent changes were made by consensus with ophthalmologists across Wales as part of the All Wales Ophthalmology group who provide advice and guidance to DRSSW on DR and referrals to HES. Subjects with DR were subdivided into two groups: non-sight-threatening DR (NSTDR) which included those with background DR and preproliferative DR (PPDR); and sight-threatening DR (STDR), that is, maculopathy and/or proliferative DR (table 1). As retinal thickening or clinically significant macular oedema is not discernible on non-stereoscopic images, maculopathy was defined as definite exudates or haemorrhages (with an unexplained VA of worse than 6/12) within one disc diameter of the fovea. Both eyes were assessed for DR and the worse grade from the two eyes used in the analysis. All persons with unassessable images in one or both eyes that had not previously been seen by an ophthalmologist were referred to HES for assessment. Where only one eye was assessable the presence or absence of DR relied on this eye as was the grading of DR if present. The National Screening Committee definition of unassessable images is used by DRSSW.³⁰

Characteristics of the study population were described using means (SD) for continuous variables with percentages for categorical variables. For comparisons, T tests and χ^2 tests were used, respectively, with a p value of <0.05 used to indicate statistical significance. Logistic regression analyses were performed to assess the association of the routinely collected variables with retinopathy status, separately for each type of diabetes. The continuous variables of age at diagnosis of diabetes and duration of diabetes were categorised to avoid assuming linearity, with different categories used for type 1 and type 2 diabetes to ensure equal distribution among the groups. For type 1 diabetes, age at diagnosis was divided into subgroups ≤ 12 yrs, 13–23 yrs and ≥ 24 yrs and diabetes duration into subgroups <10 yrs, 10–19 yrs and ≥ 20 years. For type 2 diabetes the subgroups for age at diagnosis were ≤ 55 yrs, 56–66 yrs and ≥ 67 yrs and for diabetes duration were <5 years, 5–9 years and ≥ 10 years, respectively. OR and 95% CI for each were calculated.

RESULTS

From January 2005 to November 2009, 91 393 persons with type 1 or type 2 diabetes were screened by DRSSW. The demographic characteristics of the participants are included in table 2. The overall prevalence of any DR within this population was 32.4% (95% CI 32.1% to 32.7%), NSTDR 29.0% (95% CI 28.7% to 29.3%) and STDR 3.4% (95% CI 3.3% to 3.5%). The prevalence of any DR was 56.3% in persons with type 1 diabetes and 30.9% in persons with type 2 diabetes. NSTDR prevalence was 45.1% in type 1 diabetes and 28.1% in type 2 diabetes. For STDR the prevalence in type 1 diabetes was 11.2% and in type 2 diabetes was 2.9%. The prevalence of the different categories of DR are shown in table 2.

The characteristics of subjects with and without DR at initial screening are compared in table 3, with the former group divided into NSTDR and STDR. In subjects with type 1 diabetes, those with STDR were more likely to be male, younger at the time of diagnosis, with a longer duration of diabetes and therefore older at first screening compared with those without

Table 1 A comparison of grading protocols for DR

ETDRS scale ²⁸		NSC ²⁹		DRSSW	
10	No DR	R0	No DR	R0	No DR
20–35	Very mild—mild non-proliferative DR	R1	Background DR	R1.1	Minimal background DR
				R1.2	Moderate background DR
43–53	Moderate—severe non-proliferative diabetic retinopathy	R2	Preproliferative DR	R2	Preproliferative DR
≥ 61	Proliferative DR	R3	Proliferative DR	R3	Proliferative DR
		M0	No maculopathy	M0	No maculopathy
		M1	Maculopathy	M1	Possible maculopathy
				M2	Definite maculopathy

DR, diabetic retinopathy; DRSSW, Diabetic Retinopathy Screening Service for Wales; ETDRS, Early Treatment of Diabetic Retinopathy Study; NSC, National Screening Committee (UK).

Table 2 Characteristics of study participants at the occasion of first screening event.

	Type 1 diabetes	Type 2 diabetes
n	5,003	86 390
Age, years	36.5 (16.4)	65.3 (11.7)
Gender n (%)		
Male	2721 (54.7)	48 490 (56.4)
Female	2257 (45.3)	37 446 (43.6)
Known duration of diabetes, years	16.7 (13.2)	5.3 (5.6)
Treatment of diabetes		
Diet only	0	26 025 (30.5)
OHA	0	51 071 (59.9)
Insulin	5003 (100)	8226 (9.5)
Age at diagnosis of diabetes, years	19.7 (13.7)	60.0 (11.9)
Unassessable images % (95% CI)	0.5 (0.3 to 0.7)	2.1 (2.0 to 2.2)
DR status: % (95% CI)		
No DR	43.8 (42.4 to 45.1)	69.0 (68.7 to 69.3)
BDR	39.8 (38.4 to 41.2)	26.5 (26.3 to 26.9)
PPDR only	5.2 (4.6 to 5.9)	1.5 (1.4 to 1.6)
NSTDR	45.1 (43.7 to 46.4)	28.1 (27.8 to 28.4)
Maculopathy (with BDR)	4.2 (3.7 to 4.8)	1.4 (1.3 to 1.5)
PPDR with maculopathy	2.9 (2.5 to 3.4)	0.97 (0.91 to 1.04)
PDR only	2.6 (2.2 to 3.1)	0.31 (0.28 to 0.35)
PDR with maculopathy	1.5 (1.2 to 1.9)	0.23 (0.20 to 0.27)
STDR	11.2 (10.4 to 12.1)	2.9 (2.8 to 3.0)

Some subjects had missing values for gender and treatment. Numbers are mean (\pm SD) or n (%) unless otherwise stated.

BDR, background diabetic retinopathy; diabetes, diabetes mellitus; No DR, no evidence of diabetic retinopathy; NSTDR, non-sight-threatening diabetic retinopathy; OHA, oral hypoglycaemic agent; PDR, proliferative diabetic retinopathy; PDR with maculopathy, proliferative diabetic retinopathy with exudates within 1 disc diameter of the fovea; PPDR, preproliferative diabetic retinopathy; PPDR with maculopathy, preproliferative diabetic retinopathy with exudates less than 1 disc diameter from the fovea; STDR, Sight-threatening diabetic retinopathy.

DR. Participants with type 2 diabetes and STDR were also more likely to be male, younger at the screening event and with a longer duration of diabetes, and in addition were more likely to be receiving insulin therapy compared with those without DR.

The results of the logistic regression analysis are shown in [table 4](#). For subjects with type 1 diabetes the OR for each type of DR was significantly higher in those aged 12–23 years at diagnosis and significantly lower in those aged over 23 years when compared with those aged below 12 years at diagnosis. Men also had increased odds of all severities of DR compared with women. The OR of all severity grades of DR increased sharply with duration of diabetes. There was a 7.90-fold and 20.60-fold increased odds of any DR associated with a duration of diabetes of 10–19 years and ≥ 20 years compared with <10 years and a 28.22-fold and 85.84-fold increased odds of STDR in the same subgroups, respectively. For type 2 diabetes the ORs of any DR and NSTDR were significantly higher (1.18 and 1.24, respectively) in those aged over 66 years at diagnosis of diabetes than in subjects aged 55 years or less at diagnosis. However the OR of STDR decreased (0.60 and 0.58) with increasing age at diagnosis of diabetes. Men had increased odds of all grades of DR compared with women. The odds of all grades of DR increased with increasing duration of diabetes. For any DR the odds increased by a factor of 1.60 with a known duration of diabetes of 5–9 years and almost 3.71-fold for a known duration of diabetes of 10 years or more compared with less than 5 years and for STDR the odds increased from 1.83-fold to 6.76-fold in the same subgroups, respectively. The use of insulin had ORs of 2.77 for any DR and 7.24 for STDR compared with those using diet alone.

DISCUSSION

This study provides estimates of the baseline prevalence of DR for subjects over the age of 12 years and not receiving care at the HES for DR related reasons, when attending for the first time at DRSSW. In the population studied the prevalence of any DR, NSTDR and STDR in subjects with type 1 diabetes were 56.3%, 45.0% and 11.2%, respectively, and in type 2 diabetes were 30.9%, 27.7% and 2.9%, respectively. The presence of NSTDR and STDR was strongly associated with increasing duration of diabetes with either type 1 or type 2 diabetes and was also associated with insulin therapy in those with type 2 diabetes.

The strength of this study is the large population size that underwent systematic screening using standardised quality assured procedures and equipment for photography and grading. Graders and photographers were accredited. The

Table 3 Characteristics for subjects with type 1 and type 2 diabetes presenting either without DR, with any DR, NSTDR or STDR

	Type 1 diabetes				Type 2 diabetes			
	NDR (Reference)	Any DR	NSTDR	STDR	NDR (Reference)	Any DR	NSTDR	STDR
n	2,177	2,802	2,243	559	58 389	26 216	23 763	2,453
Age years	34.5 (19.2)	37.9 (13.5)*	37.5 (14.0)*	39.1 (11.5)*	64.6 (11.7)	66.3 (11.4)*	66.6 (11.5)*	64.0 (10.9)*
Gender						*	*	*
Male	1182 (54.5)	1524 (54.7)	1170 (52.5)	354 (63.4)*	32 162(55.4)	15 425(59.1)	13 908(58.8)	1517 (62.0)
Female	985 (45.5)	1264 (45.3)	1060 (47.5)	204 (36.6)	25 886(44.6)	10 684(40.9)	9753 (41.2)	931 (38.0)
Duration of diabetes years	9.4 (10.5)	22.3 (12.2)*	21.9 (12.6)*	24.2 (10.5)*	4.3 (4.5)	7.6 (6.8)*	7.4 (6.6)*	10.4 (7.5)*
Treatment of diabetes					*	*	*	*
Diet only	N/A	N/A	N/A	N/A	20 379(35.3)	5078 (19.6)	4873 (20.8)	205 (8.5)
OHA	N/A	N/A	N/A	N/A	33 578(58.2)	16 446(63.6)	14 941(63.7)	1505 (62.0)
Insulin	N/A	N/A	N/A	N/A	3744 (6.5)	4339 (16.8)	3625 (15.5)	714 (29.5)
Age at diagnosis of diabetes years	25.2 (17.2)	15.5 (7.9)*	15.7 (7.9)*	14.9 (7.9)*	60.3 (11.7)*	58.7 (12.1)*	59.2 (12.0)*	53.5 (11.8)*

Numbers are mean (\pm SD) or n (%).

*p Values <0.0001.

Any DR, any diabetic retinopathy; diabetes, diabetes mellitus; N/A, not applicable; NDR, no evidence of diabetic retinopathy; NSTDR, non-sight-threatening diabetic retinopathy; OHA, oral hypoglycaemic agent; STDR, sight-threatening diabetic retinopathy.

Table 4 Multivariate logistic regression analysis for the association between age, gender and duration of diabetes with the presence of any DR, NSTDR and STDR in persons with type 1 and type 2 diabetes

Type 1 diabetes	n	Any DR OR (95% CI)	NSTDR OR (95% CI)	STDR OR (95% CI)	Type 2 diabetes	n	Any DR OR (95% CI)	NSTDR OR (95% CI)	STDR OR (95% CI)
Age at diagnosis of diabetes years									
≤12	1,725	1.00	1.00	1.00	≤55	30 184	1.00	1.00	1.00
13–23	1,703	1.34 (1.12 to 1.58)	1.30 (1.09 to 1.55)	1.26 (0.95 to 1.66)	56–66	29 437	0.97 (0.94 to 1.01)	1.01 (0.98 to 1.05)	0.60 (0.54 to 0.66)
≥24	1,575	0.40 (0.34 to 0.47)	0.40 (0.33 to 0.47)	0.30 (0.22 to 0.40)	≥67	26 599	1.18 (1.13 to 1.22)	1.24 (1.19 to 1.29)	0.58 (0.51 to 0.66)
Male	2,721	1.20 (1.04 to 1.38)	1.14 (0.99 to 1.32)	2.02 (1.58 to 2.57)	Male	48 490	1.17 (1.14 to 1.21)	1.16 (1.12 to 1.20)	1.26 (1.16 to 1.38)
Duration of diabetes years									
<10	1,876	1.00	1.00	1.00	<5	49 390	1.00	1.00	1.00
10–19	1,341	7.90 (6.69 to 9.32)	6.74 (5.68 to 8.00)	28.22 (18.04 to 44.15)	5–9	21 592	1.60 (1.54 to 1.66)	1.59 (1.53 to 1.65)	1.83 (1.63 to 2.06)
≥20	1,786	20.60 (17.26 to 24.59)	16.91 (14.10 to 20.28)	85.84 (55.20 to 133.50)	≥10	15 238	3.71 (3.56 to 3.87)	47 (3.33 to 3.63)	6.76 (6.07 to 7.53)
Treatment of diabetes									
					Diet	26 025	1.00	1.00	1.00
					OHA	51 071	1.59 (1.53 to 1.65)	1.54 (1.48 to 1.60)	2.96 (2.55 to 3.45)
					Insulin	8,226	2.77 (2.61 to 2.94)	2.55 (2.40 to 2.71)	7.24 (6.10 to 8.59)

No DR is the reference group. NSTDR group excludes STDR and STDR group excludes NSTDR.
Any DR, any diabetic retinopathy; diabetes, diabetes mellitus; NSTDR, non-sight-threatening diabetic retinopathy; OHA, oral hypoglycaemic agent; STDR, sight-threatening diabetic retinopathy.

exclusion of subjects who did not participate in screening is a limitation. The exclusion of those persons with diabetes under the care of HES because of DR is likely to lead to an underestimation, however currently the extent of this difference is not known. Although PPDR is the level at which referral to HES is required by screening programmes in the UK, it was excluded from the category of STDR in this study so that it was more comparable with the category of STDR reported in previous studies. Also the limited availability of putative risk factors which included only duration and treatment of diabetes with glycaemic control, blood pressure and lipid status not collected by the DRSSW is a limitation and will be addressed in future studies.

The comparison of the prevalence rates for DR between studies is inherently difficult due to the changing classification of diabetes over time and the different grading protocols employed, as well as differences in population characteristics.^{8 27 31–34} Web appendix 1 shows the prevalence rates found in previous studies worldwide. In other UK screening programmes the prevalence of any DR has been reported at 53.5% for type 1 diabetes,³³ and 19.2–25.3% for type 2 diabetes,^{3 32 33} which were lower than that seen in our study population at 56.0% and 30.3%, respectively. Also in comparison, in Iceland the prevalence of DR was slightly lower in type 1 diabetes and higher in type 2 diabetes at 51.7%³⁴ and 41.0%,³¹ respectively. A recent meta-analysis found a much higher prevalence of DR in type 1 diabetes at 77.3%²⁷ and a slightly lower prevalence in type 2 diabetes at 25.2%.²⁷ Retinal image capture (number of images and the use or not of mydriasis) may contribute to some of these differences as well as duration of diabetes. Our study clearly demonstrates that increased duration of diabetes is associated with a higher prevalence of DR. The prevalence of STDR previously reported in the UK has been 16.4% in type 1 diabetes and 1.9% and 6.0% in type 2 diabetes.^{3 32 33} In our study the prevalence of STDR was a little lower in persons with type 1 diabetes at 11.2%. Differences in the classification of STDR such as the inclusion or exclusion of PPDR and definitions of maculopathy may explain the differences.^{32 33} We had essentially similar prevalence of STDR at 2.9% in type 2 diabetes. The Scottish screening programme reported the prevalence in 47 090 newly diagnosed type 2 diabetes and this short duration is likely to be the reason for the low prevalence of DR reported at 19.3% for any DR and 1.9% for RDR.³

Increasing duration of diabetes was the most significant risk factor for the presence of any DR, NSTDR and STDR in subjects with type 1 and type 2 diabetes. The ORs were much higher in type 1 diabetes compared with type 2 diabetes, however the duration of diabetes was also longer with subgroups of <10 years, 10–19 years and ≥20 years compared with <5 years, 5–9 years and ≥10 years, respectively. The risk of all grades of DR increased with duration of diabetes being particularly high in those with diabetes duration of 20 years or more for type 1 diabetes and 10 years or more for type 2 diabetes.

In our study we observed an increased risk of all severities of DR associated with the use of insulin after adjusting for all other confounders. For type 2 diabetes this may reflect a more advanced disease state and we interpret this as likely to be an epiphenomenon and not a direct result of insulin therapy. Glycaemia and duration of diabetes have previously been shown to be highly associated with the presence of DR along with elevated blood pressure and cholesterol levels.^{4 8 33 35–38}

To date this study represents the largest reported community-based national DR screening programme for detecting the presence of DR, especially STDR. The findings will provide our policy makers with important information for planning eye care services, with the proviso that the prevalence of STDR may be underestimated because of those already within HES. The strong association with disease duration demonstrates the importance of early detection and referral to a screening programme. The detection of STDR at an early stage is essential to ensure timely onward referral for further assessment and possible treatment to improved outcome. Detection of NSTDR provides the physician with an opportunity to improve, where necessary, glycaemic and blood pressure control to prevent the progression of DR. A structured screening programme is expected to reduce blindness by 40% within 4 years.²⁹ Addressing issues of non-attendance currently at approximately 20% will contribute greatly to the success of such programmes to ensure optimal cost benefit of any DR screening service, especially poignant in times of austerity.

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Competing interests None.

Ethics approval All data from those persons who consented at screening for their anonymous data to be used in research was anonymised at source by the data manager prior to being provided to the study team for analysis. R&D and ethics approval was sought for this study; however both panels decided the study was a service evaluation and not research and as such R&D and ethical approval was not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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Prevalence of diabetic retinopathy within a national diabetic retinopathy screening service

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Appendix 4 Conference presentations list

June 2010

American Diabetes Association (ADA) 70th Scientific Sessions (Poster)

Determining a safe screening interval for subjects without diabetic retinopathy

Thomas R.L., Roy Chowdhury S., Luzio S.D., Hale S.L., North R.V., Owens D.R.

Diabetic Retinopathy status at First Screening Visit in a National Screening Program, Wales UK

Roy Chowdhury S., **Thomas R.L.**, Luzio S.D., Hale S.L., North R.V., Owens D.R.

September 2010

European Association of the Study of Diabetes (EASD) 46th Annual Meeting (Poster)

Prevalence of Diabetic Retinopathy at first screening event in a National screening programme in Wales UK: 2005-2009

Roy Chowdhury S., **Thomas R.L.**, Luzio S.D., Hale S.L., North R.V., Owens D.R.

November 2010

South Western Ophthalmological Society (Poster)

Determining a safe screening interval for subjects without diabetic retinopathy

Thomas R.L., Roy Chowdhury S., Luzio S.D., Hale S.L., North R.V., Owens D.R.

Awarded Best poster prize

Diabetic Retinopathy status at First Screening Visit in a National Screening Program, Wales UK

Roy Chowdhury S., **Thomas R.L.**, Luzio S.D., Hale S.L., North R.V., Owens D.R.

June 2011

American Diabetes Association 71st Scientific Sessions (Publication only)

Prevalence of Diabetic Retinopathy in a Diabetes and Endocrinology Centre (CDE) in South Africa (SA)

Roy Chowdhury S., **Thomas R.L.**, Distiller L.A, Brown V., Kramer B.D., Luzio S.D., Owens D.R.

Development of Diabetic Retinopathy in subjects attending a Diabetes and Endocrinology clinic in Johannesburg- South Africa

Thomas R.L., Roy Chowdhury S., Distiller L.A., Brown V., Kramer B.D., Luzio S.D., Owens D.R.

March 2011

Diabetes UK annual professional conference (Oral)

Prevalence of Diabetic Retinopathy and Distribution of Visual Acuities across Wales: 2005-2009

Thomas R.L., Roy Chowdhury S., Luzio S.D., Hale S.L., North R.V., Owens D.R.,

September 2014

Annual Wales Public Health Conference (Poster)

Incidence of Diabetic Retinopathy within the Diabetic Retinopathy Screening Service for Wales (DRSSW) - Determining safe screening intervals

Thomas R.L., Dunstan F.D., Luzio S.D., Owens D.R.,